Structural DNA nanotechnology

a.k.a. DNA carpentry

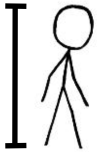
a.k.a. DNA self-assembly

ECS 232: Theory of Molecular Computation, UC Davis


Ljubljana Marshes Wheel. 5k years old

Building things


Newgrange, Ireland. 5.2k years old

Building things by hand: use tools! Great for scale of $10^{\pm 2} \times$ 

[slides credit: Damien Woods]

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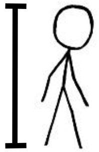
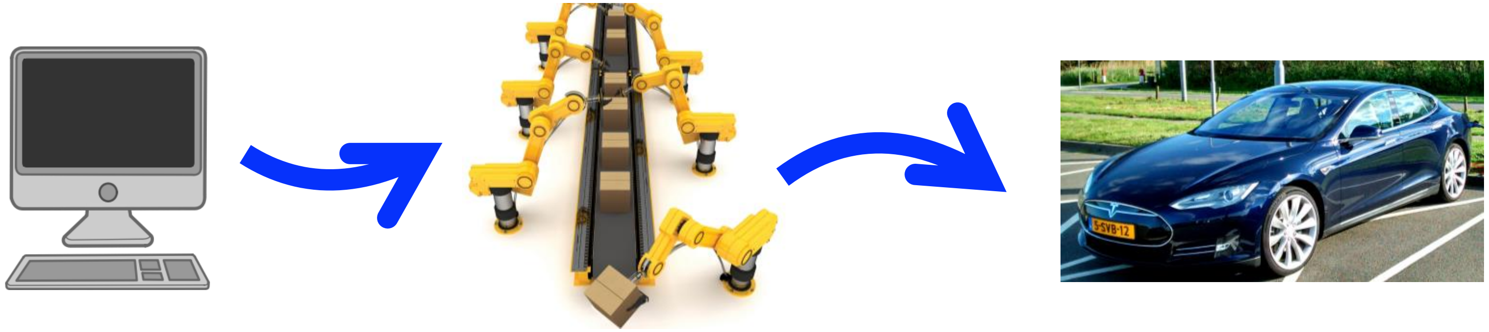
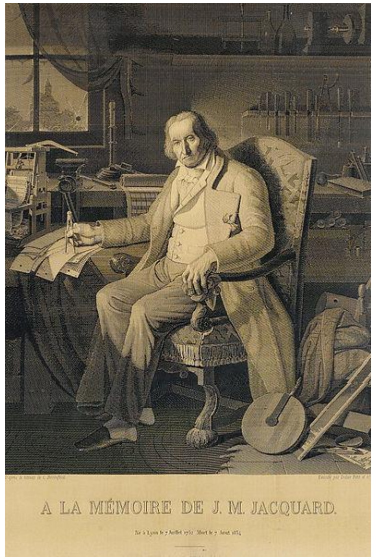
Building things by hand: use tools! Great for scale of $10^{\pm 2} \times$ 

Building tools that build things: specify target object with a computer program





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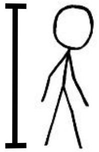
Building things by hand: use tools! Great for scale of $10^{\pm 2}$ × 

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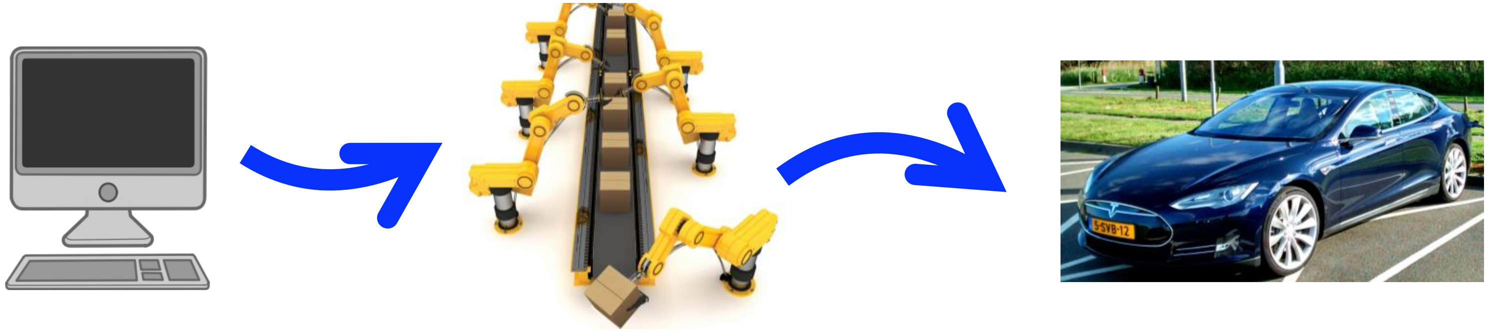
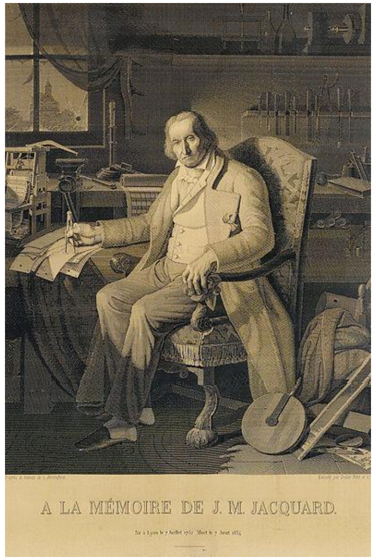
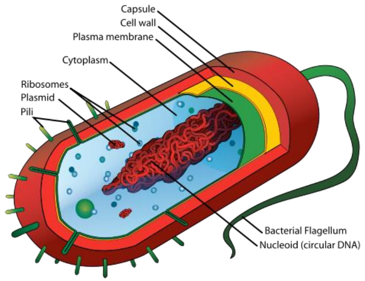




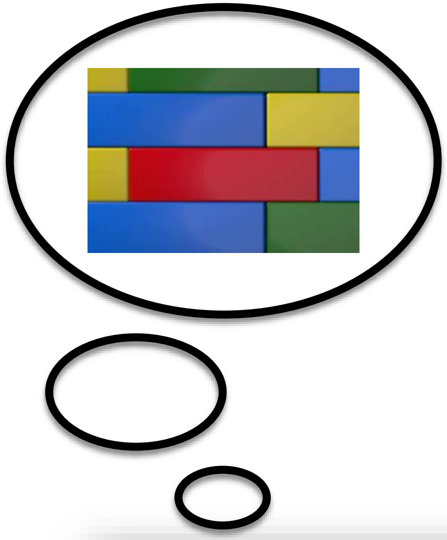
Programming **things to build themselves**: for building in small wet places where our hands or tools can't reach



Mariana Ruiz Villarreal

[slides credit: Damien Woods]

Things that build themselves

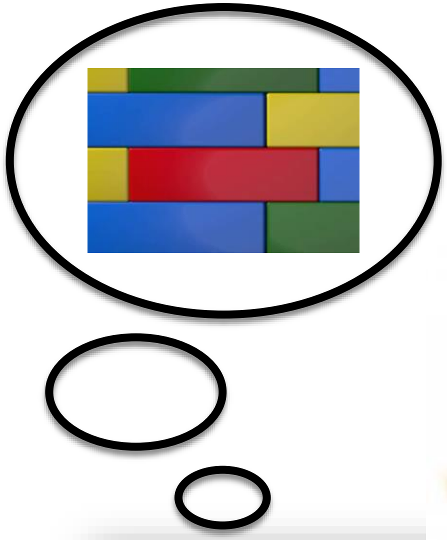


I want to stick below blue & yellow and above blue & green

Our topic: self-assembling molecules that compute as they build themselves

[slides credit: Damien Woods]

Things that build themselves



Our topic: self-assembling molecules that compute as they build themselves

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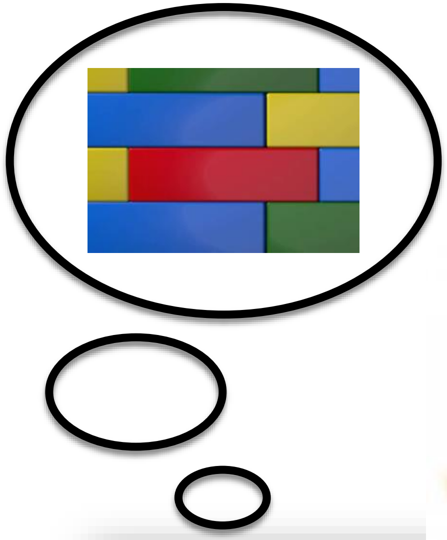
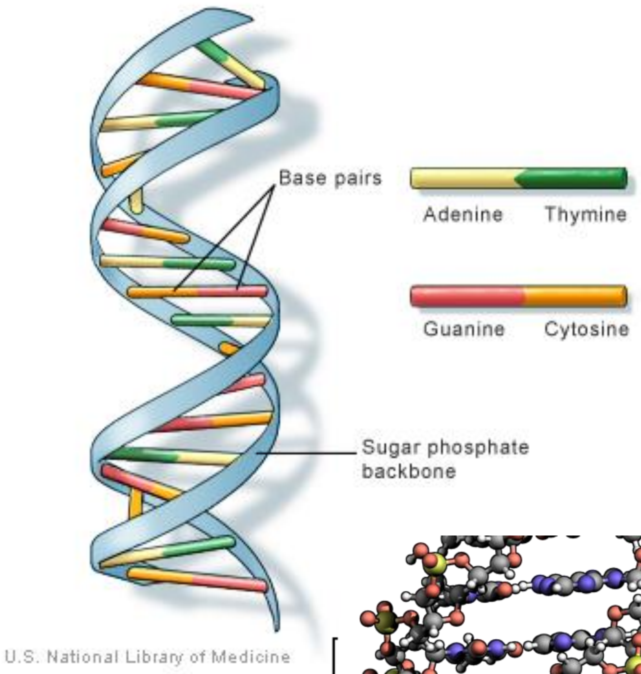
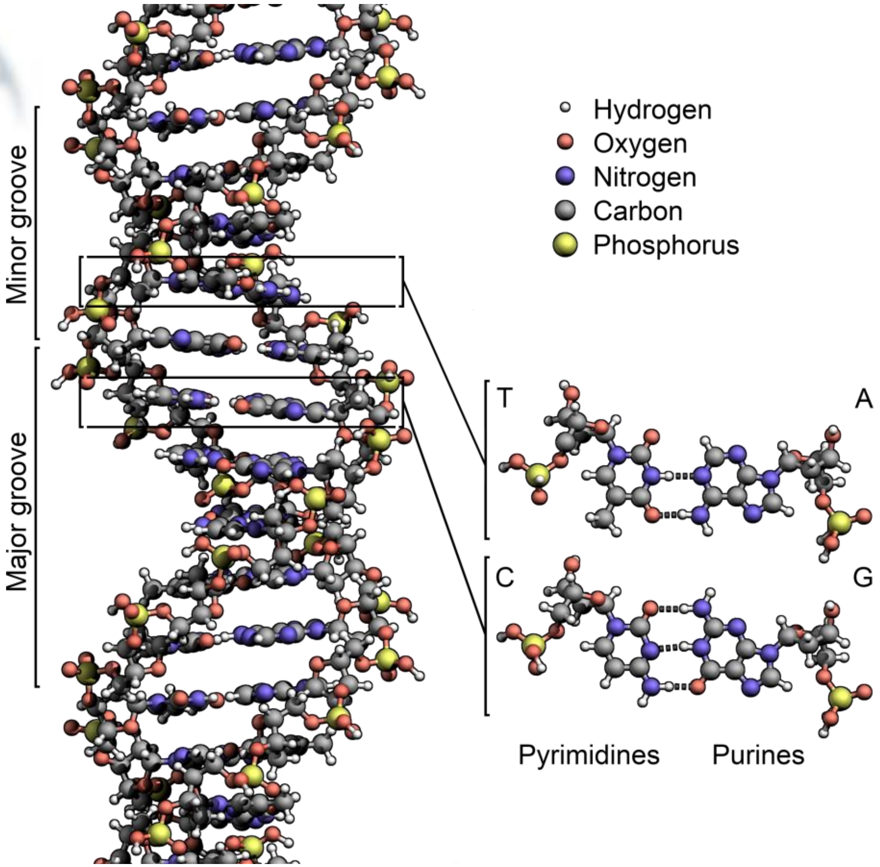


Things that build themselves

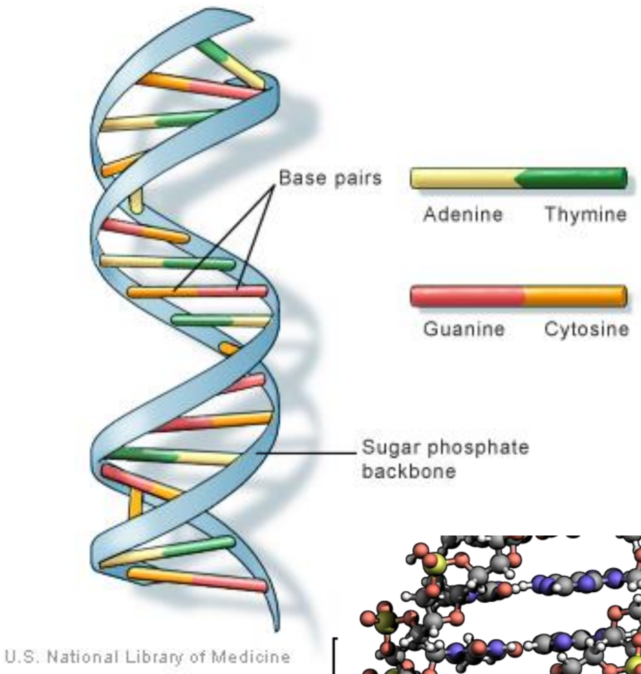
Our topic: self-assembling molecules that compute as they build themselves

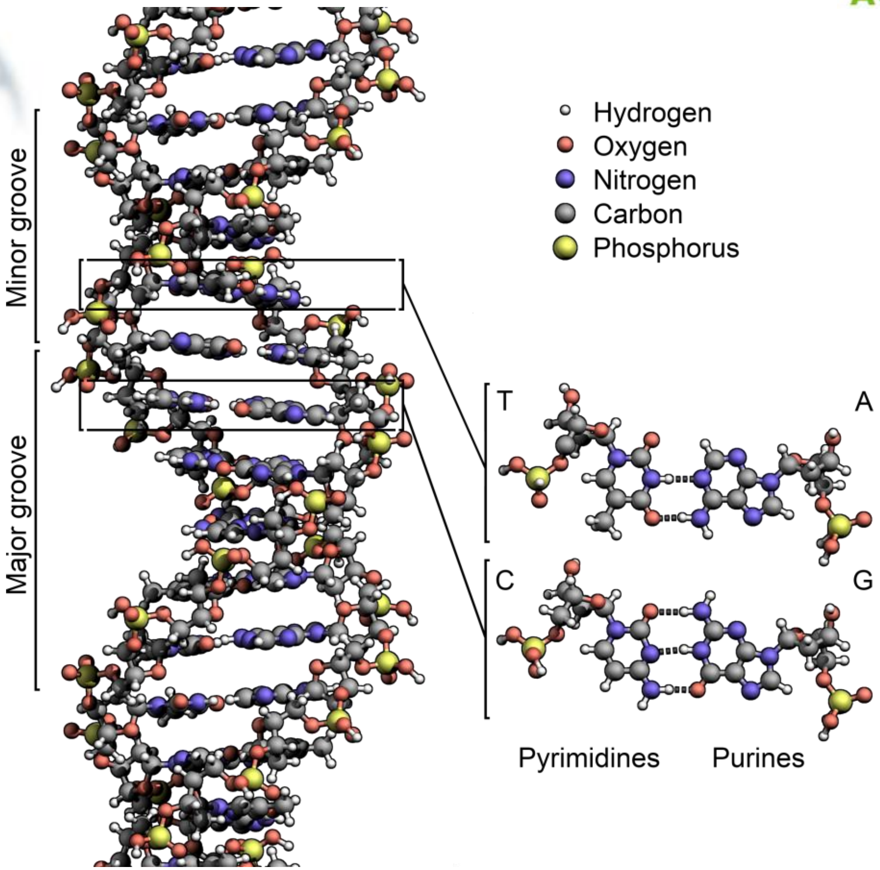
DNA as a building material





DNA as a building material



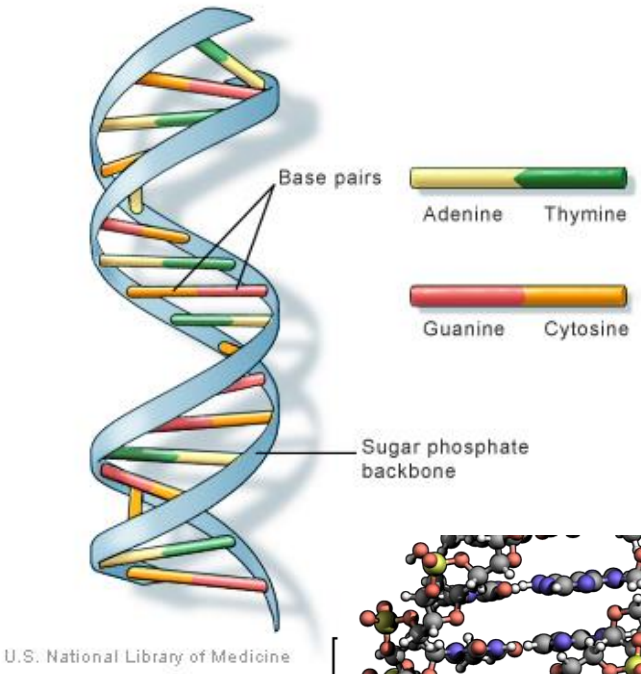


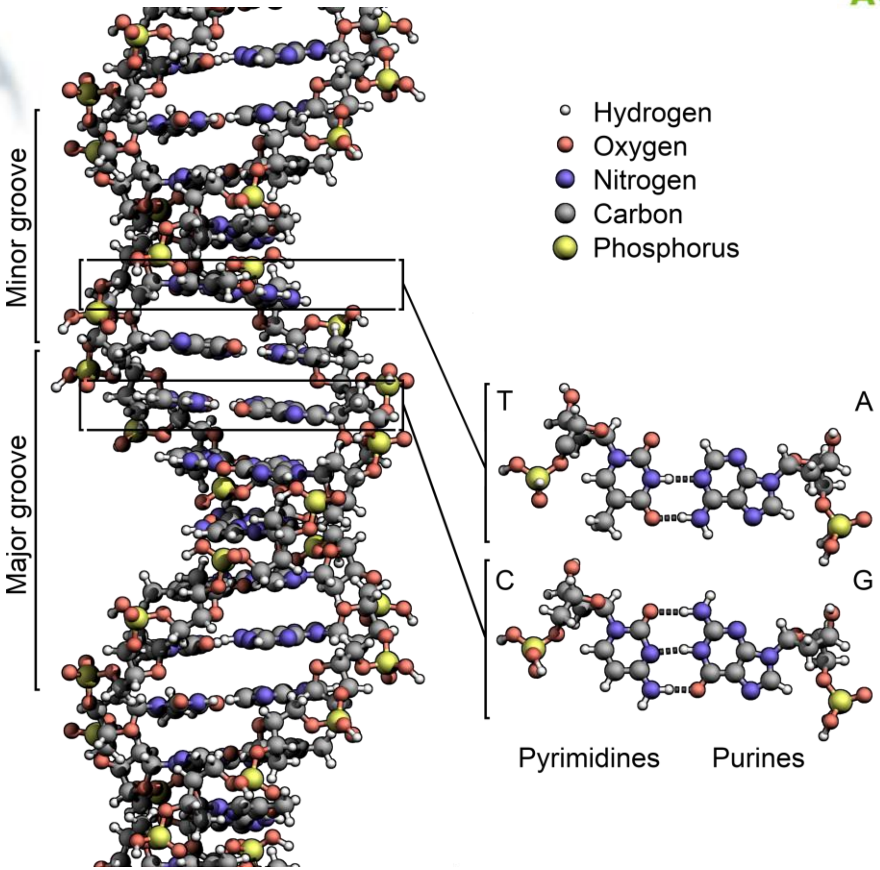
=

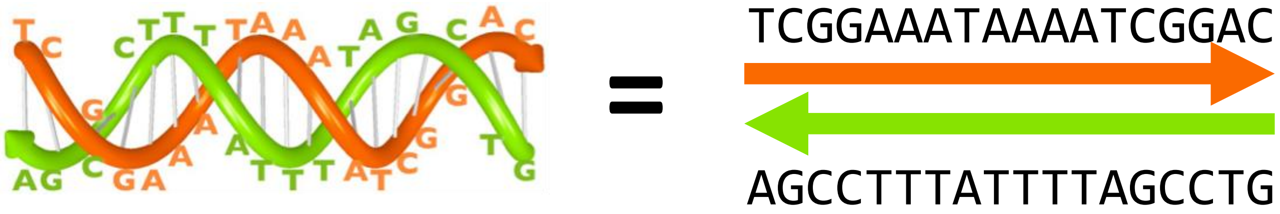
TCGGAAATAAAATCGGAC

AGCCTTTATTTTAGCCTG

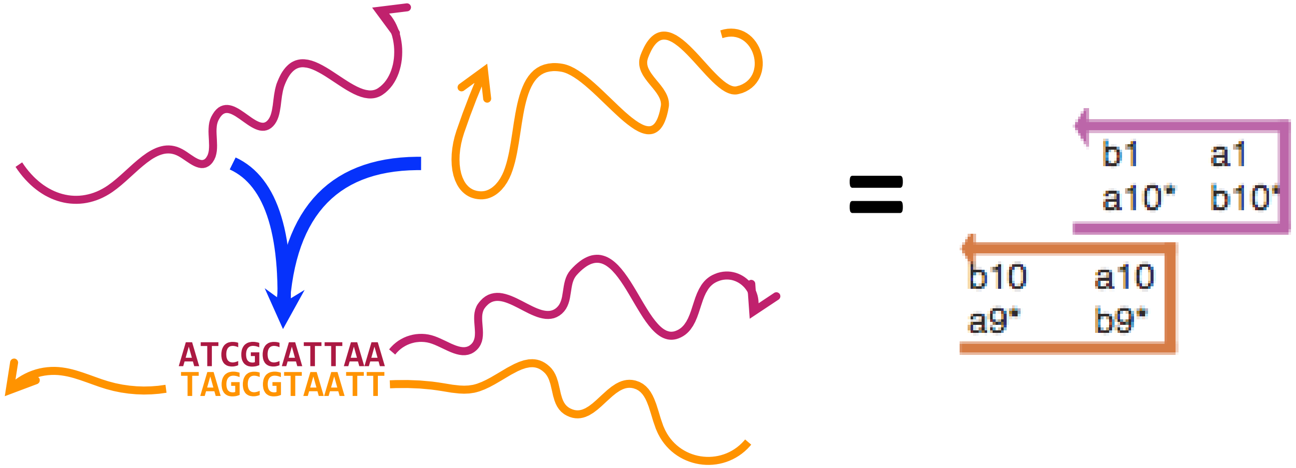
DNA as a building material







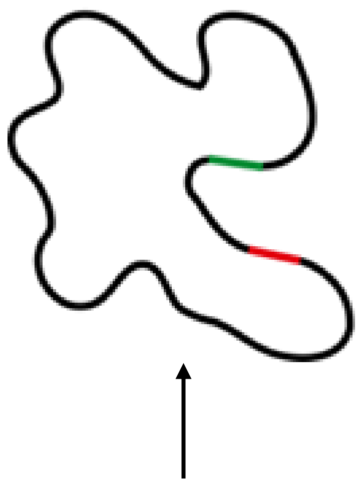
DNA strands bind even if only *part* of strands are complementary:



DNA origami

Paul Rothemund
Folding DNA to create nanoscale shapes and patterns
Nature 2006

DNA origami



scaffold DNA strand

(M13mp18 bacteriophage virus)

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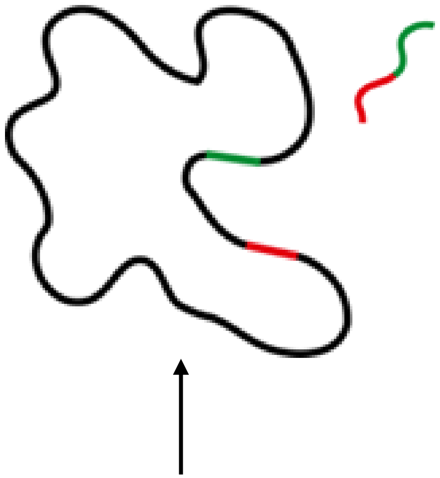

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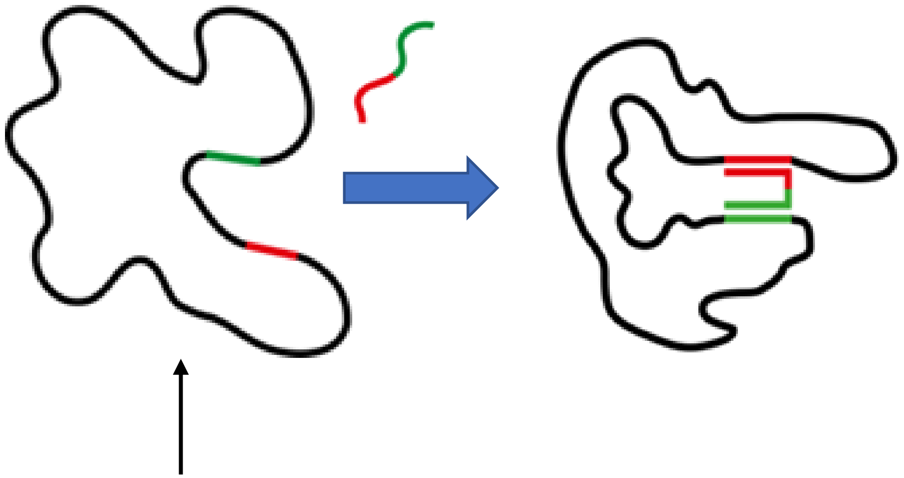

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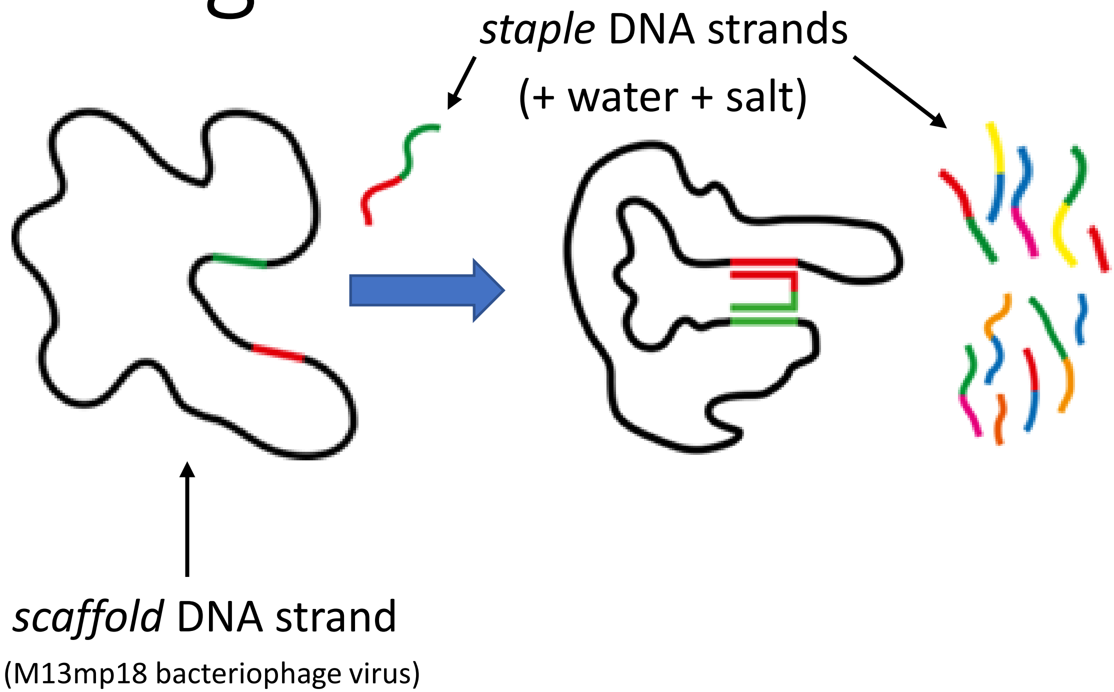

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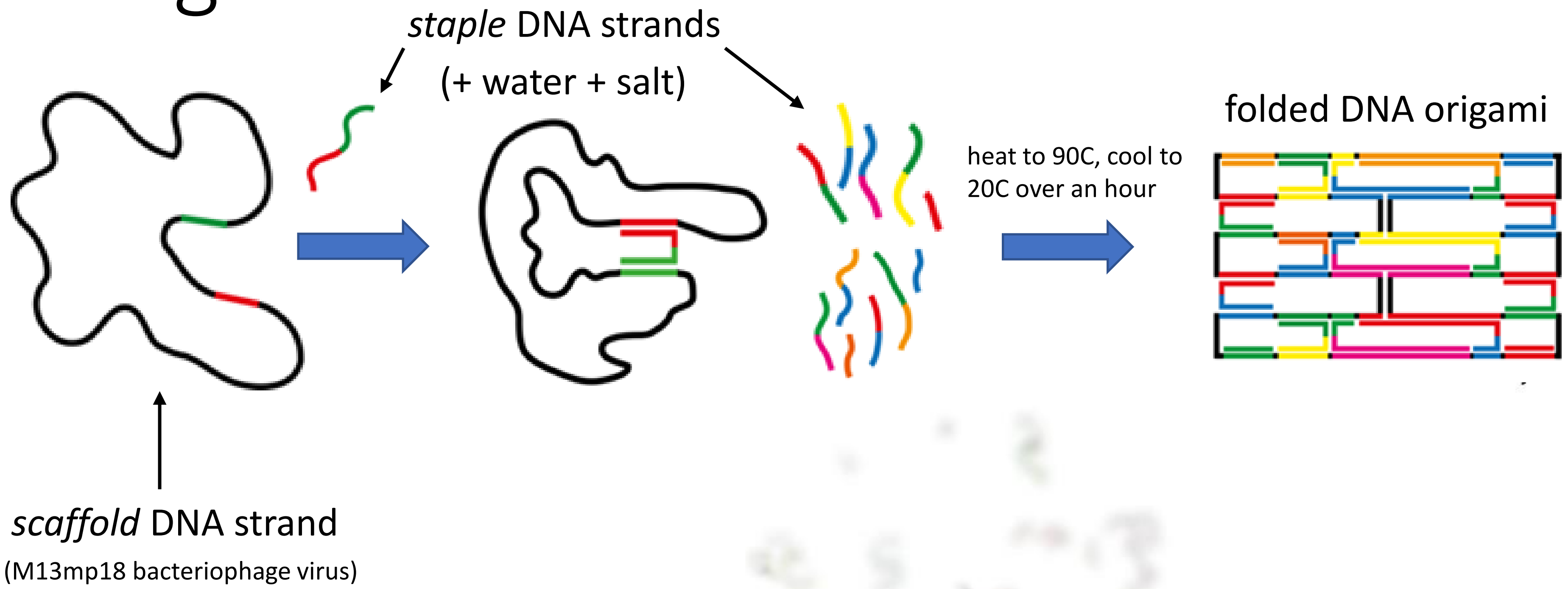

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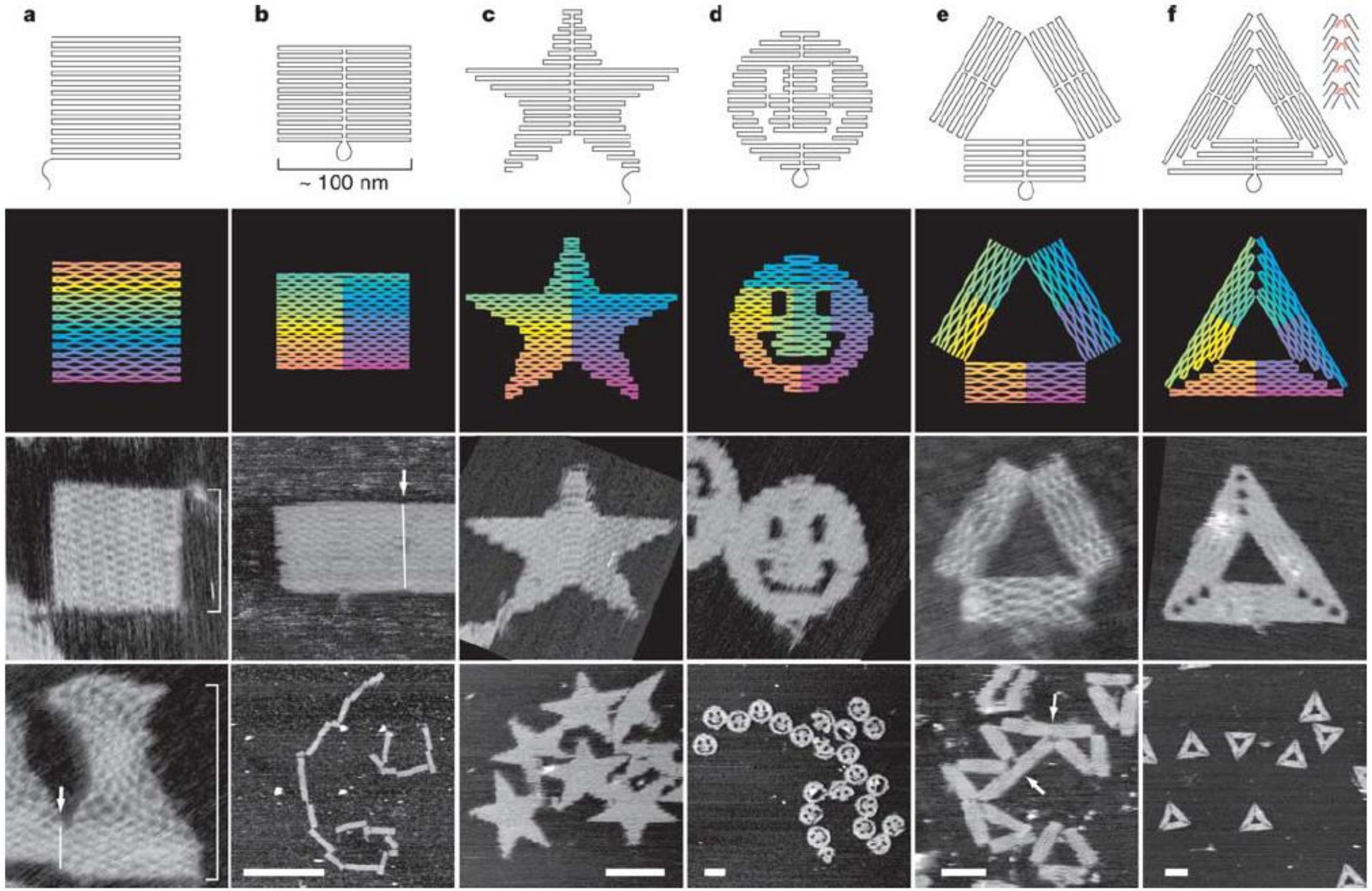
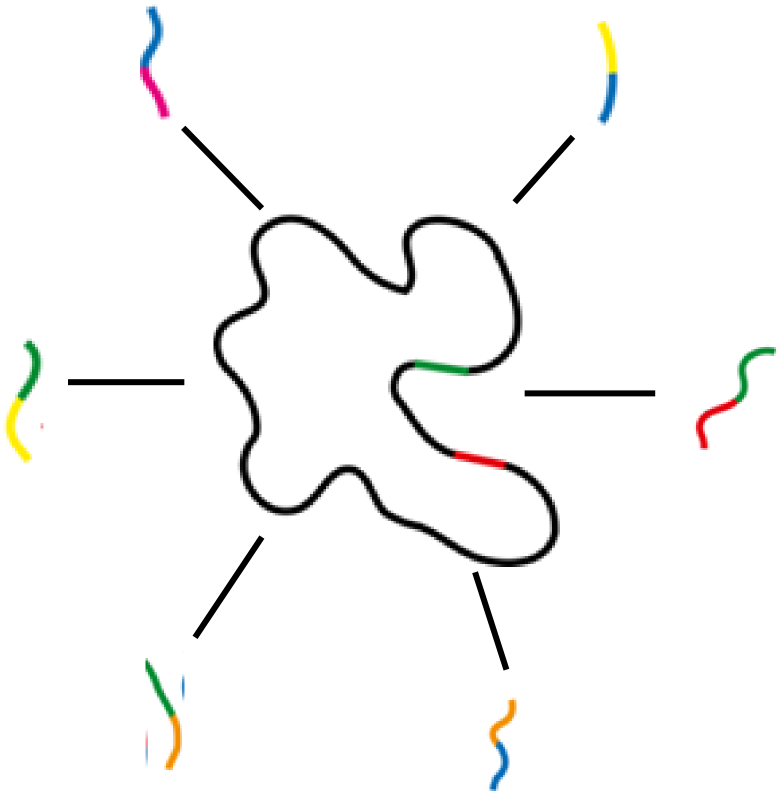


Atomic force microscope images

100 nm

Binding graphs

DNA origami: **star graph**
(all binding is between staples and scaffold)



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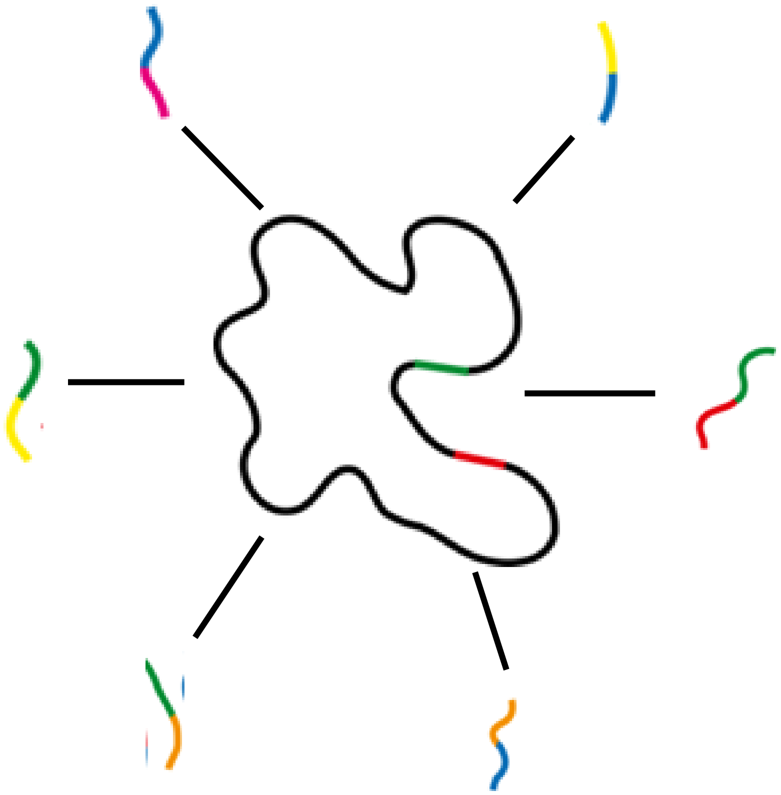
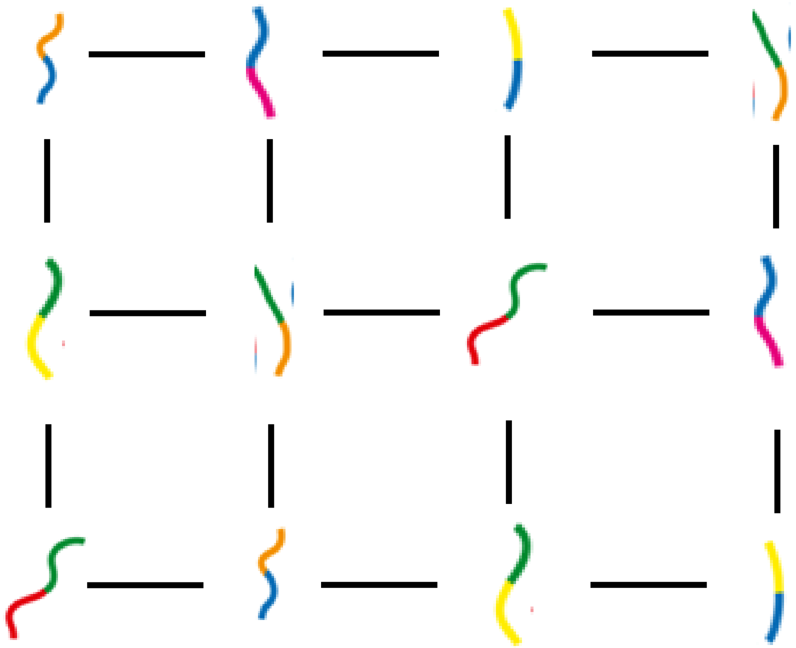


DNA tiles: **grid graph**
(tiles bind to each other, each has ≤ 4 neighbors)

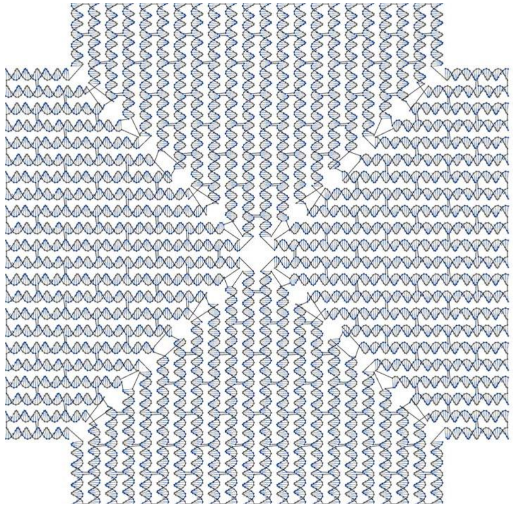


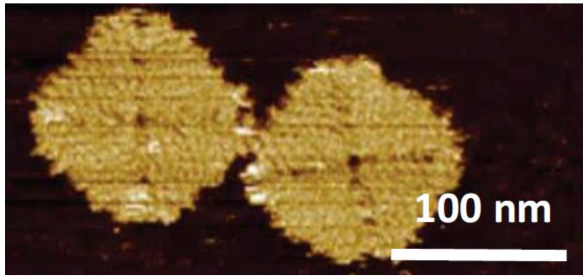
DNA tile self-assembly

DNA tile self-assembly

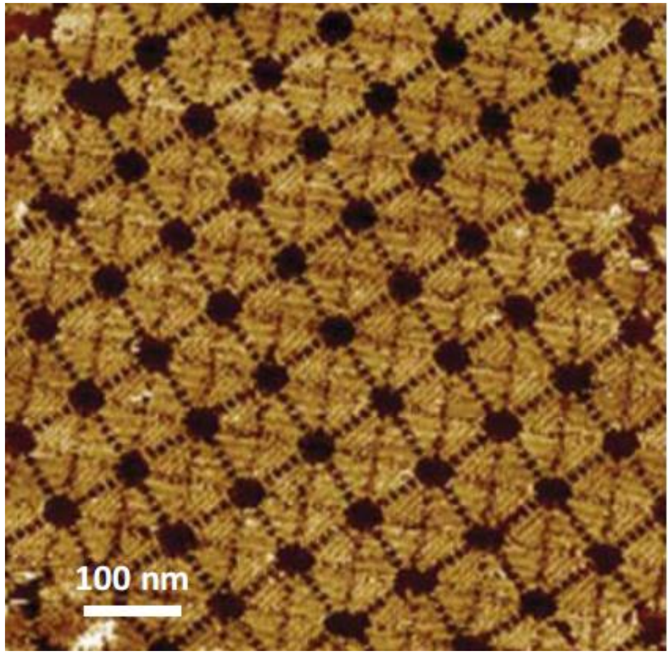
monomers ("tiles" made from DNA) bind into a crystal lattice

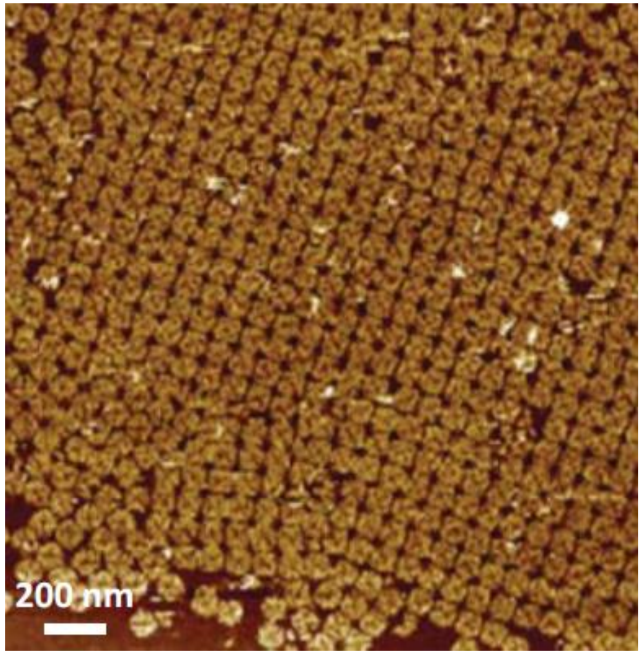
tile





lattice

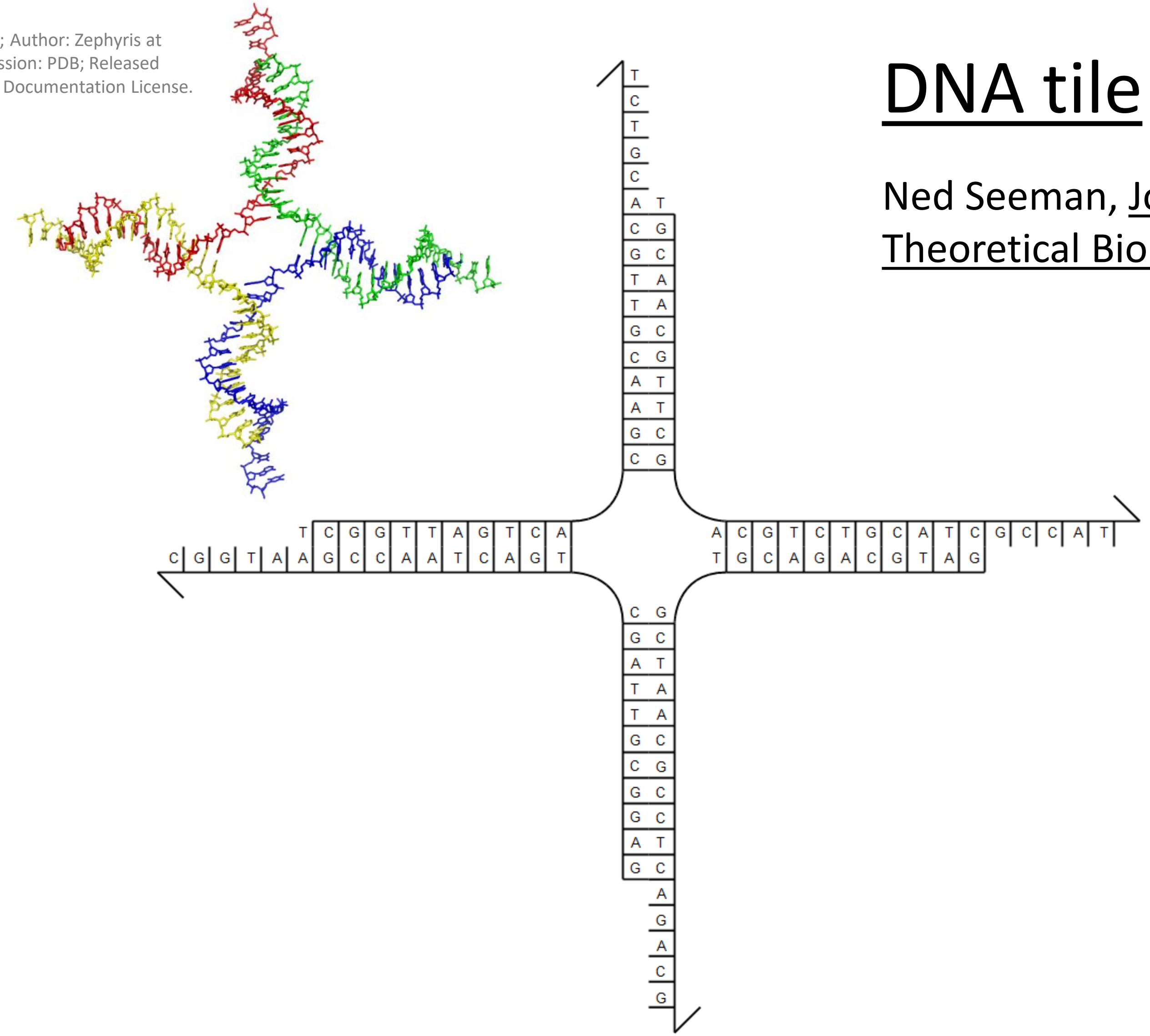




Source: *Programmable disorder in random DNA tilings*. Tikhomirov, Petersen, Qian, Nature Nanotechnology 2017

Practice of DNA tile self-assembly

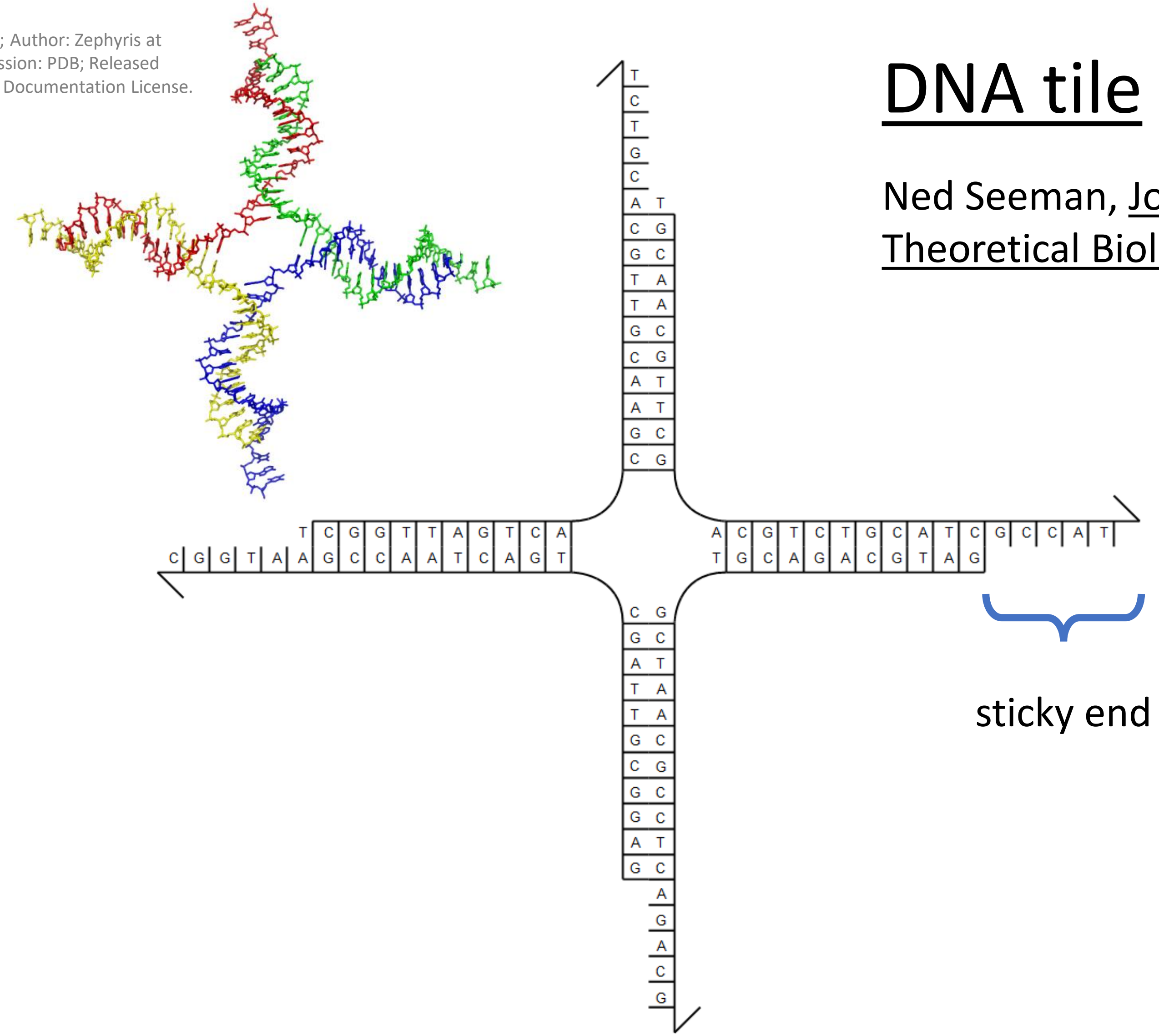
Source:en.wikipedia; Author: Zephyris at en.wikipedia; Permission: PDB; Released under the GNU Free Documentation License.



DNA tile

Ned Seeman, Journal of Theoretical Biology 1982

Practice of DNA tile self-assembly



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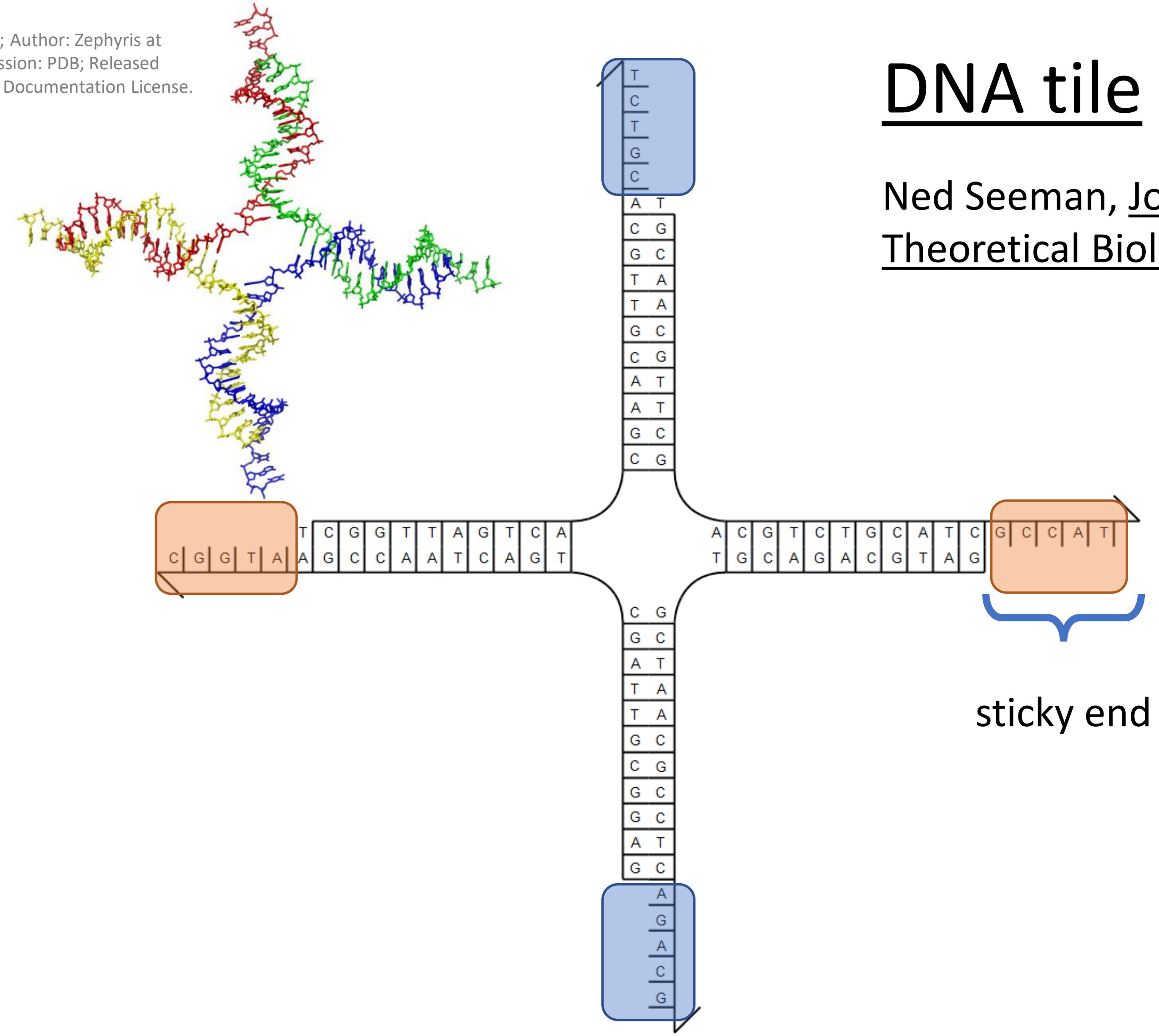

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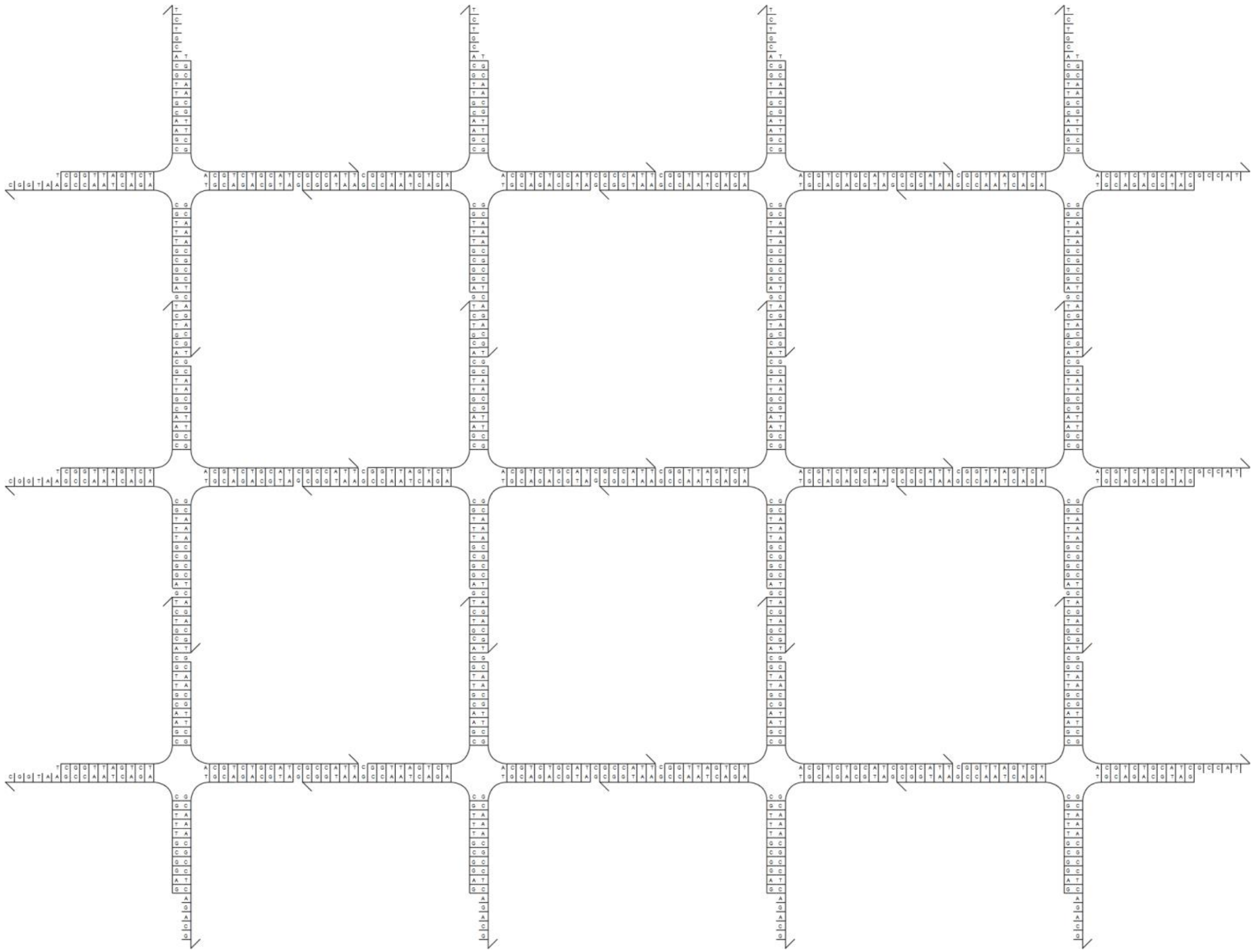
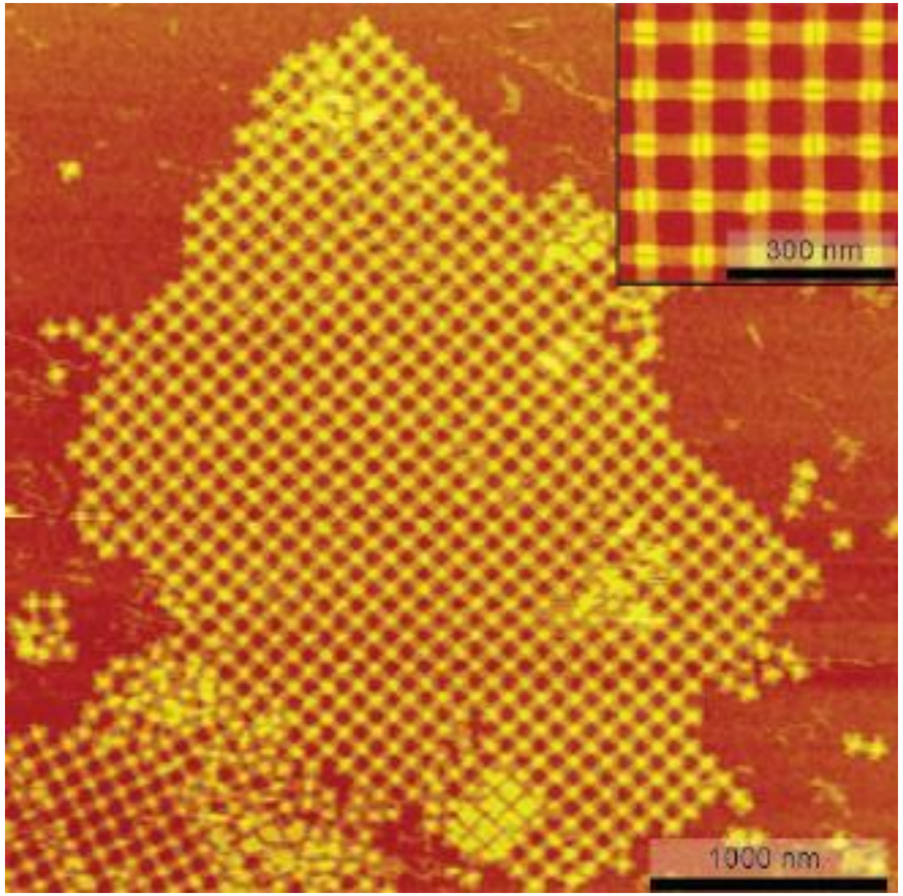
Practice of DNA tile self-assembly

Place many copies of DNA tile in solution…



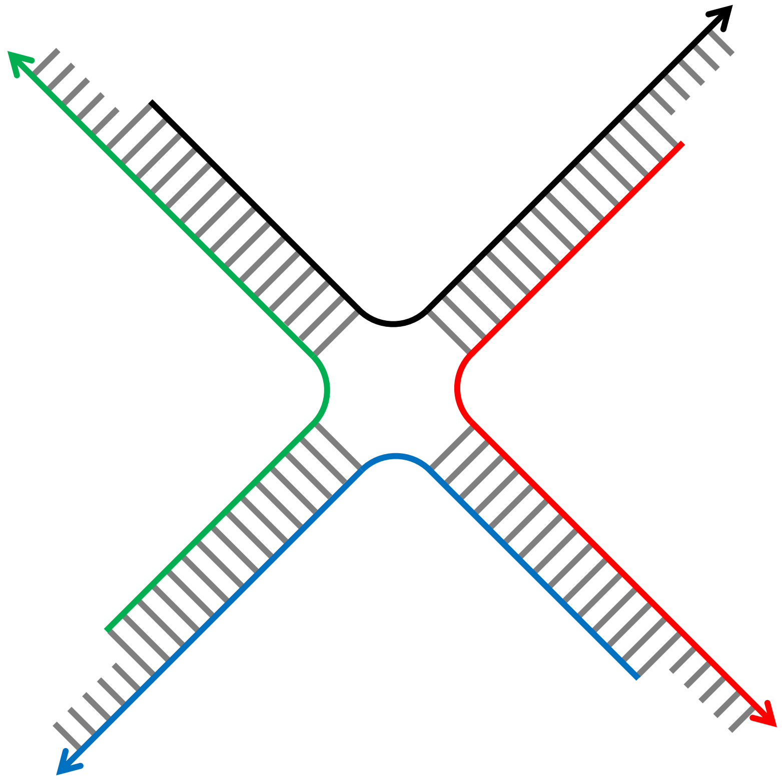
(not the same tile motif in this image)



Liu, Zhong, Wang, Seeman, Angewandte Chemie 2011

Practice of DNA tile self-assembly

What really happens in practice to Holliday junction (“base stacking”)



Practice of DNA tile self-assembly

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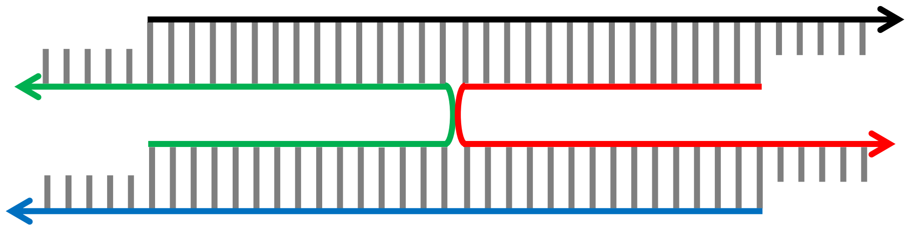

Practice of DNA tile self-assembly

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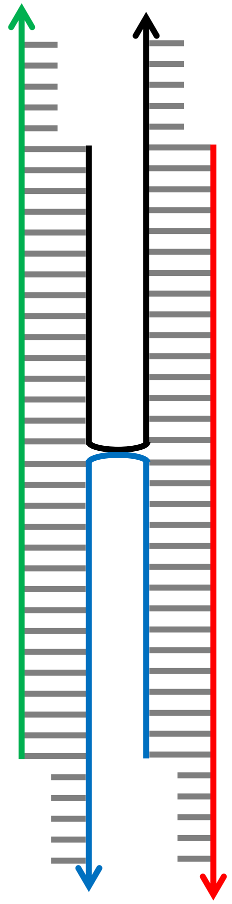

Practice of DNA tile self-assembly

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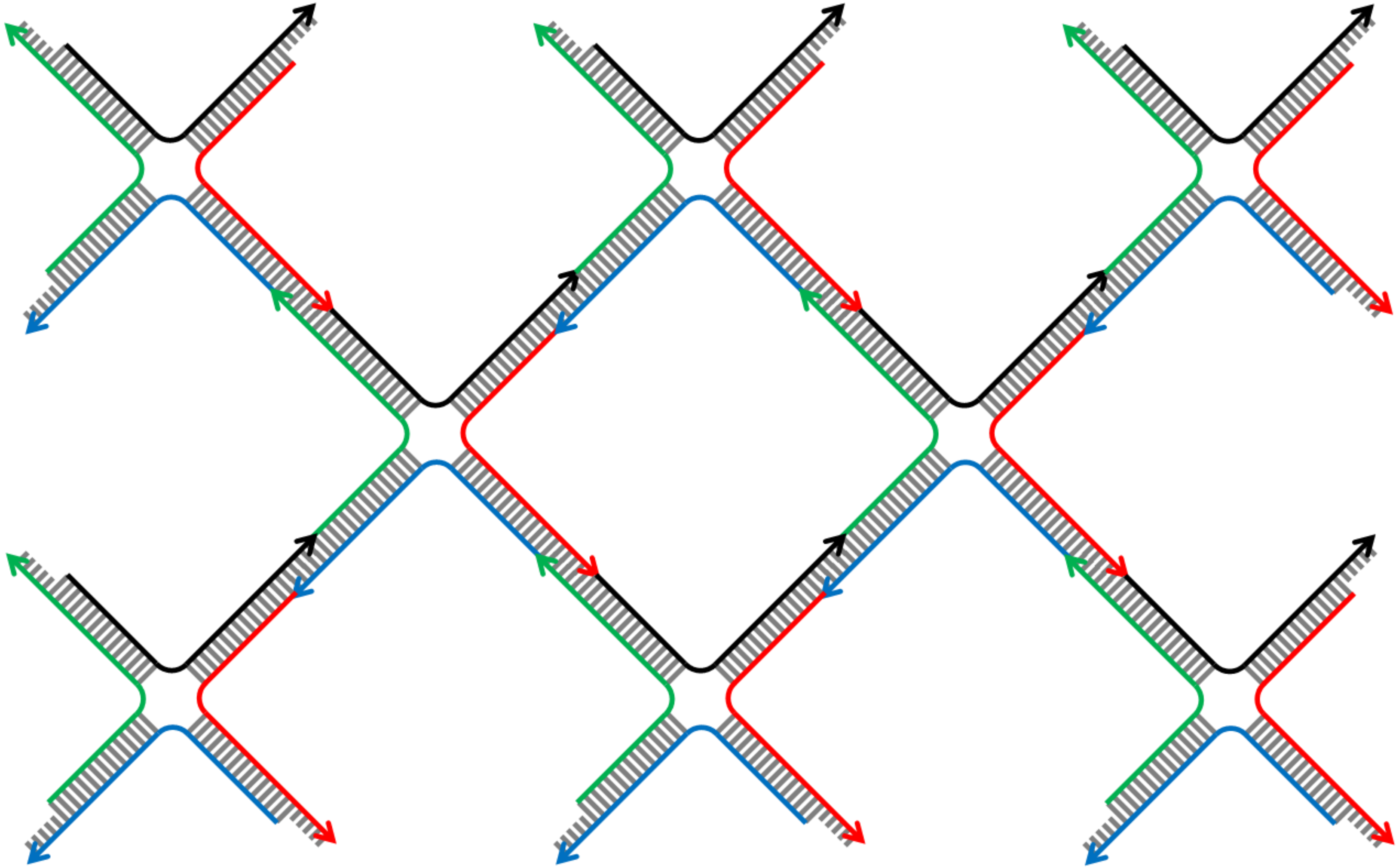

Practice of DNA tile self-assembly

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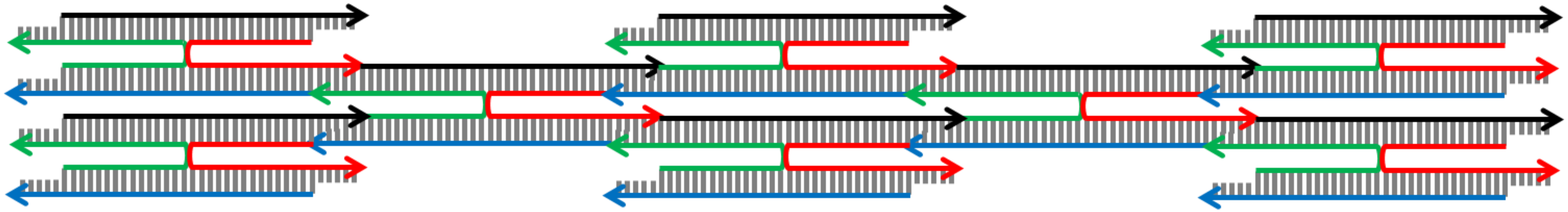
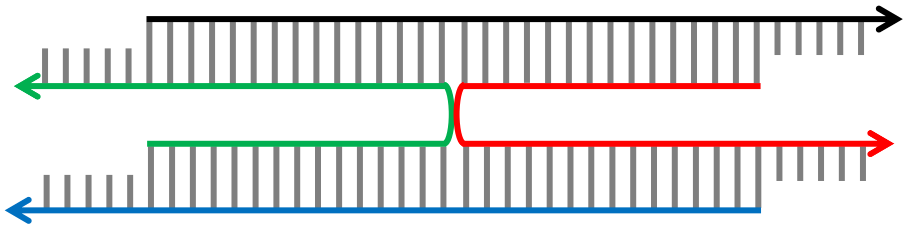
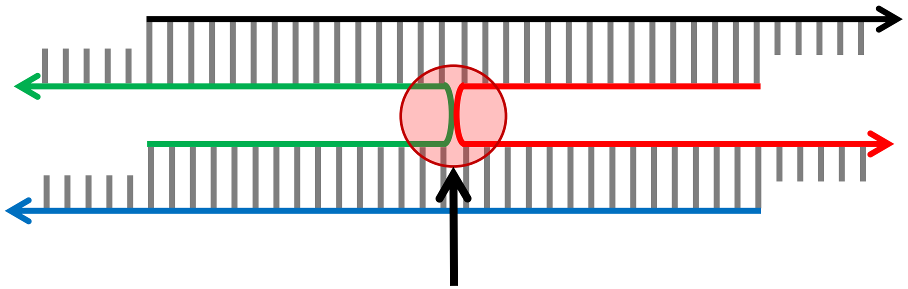


Practice of DNA tile self-assembly

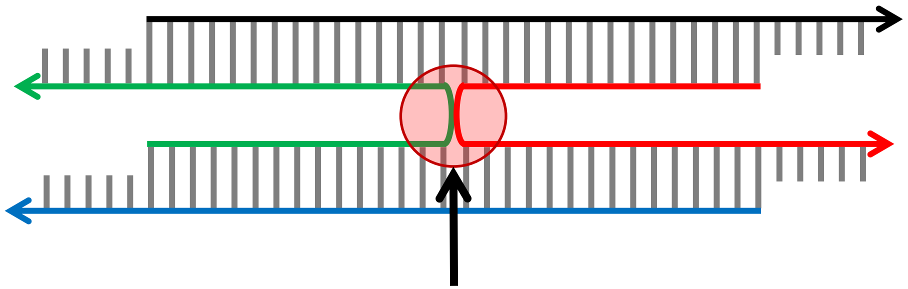


Practice of DNA tile self-assembly



single *crossover*

Practice of DNA tile self-assembly



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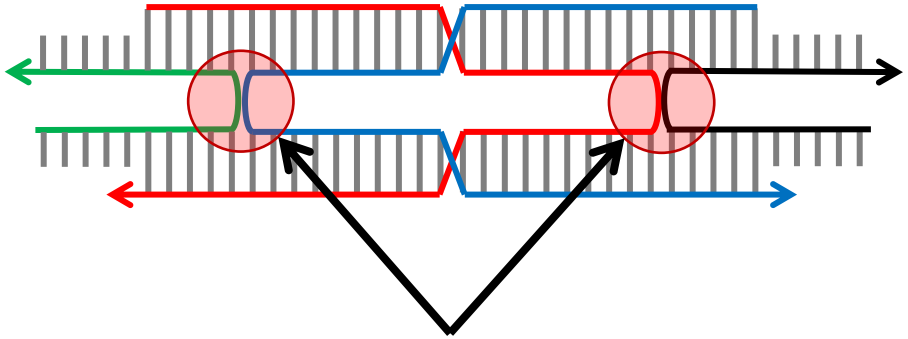


double crossover

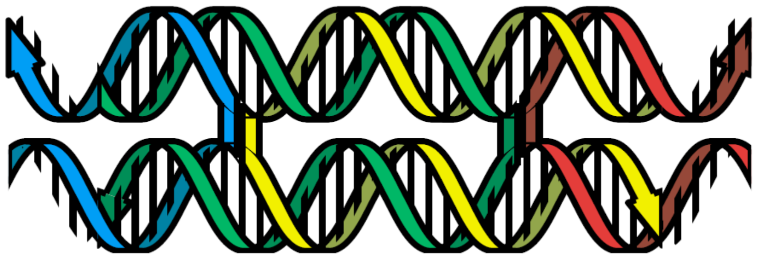
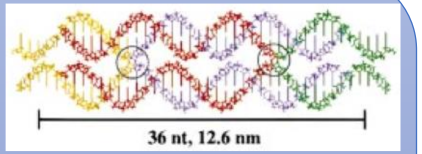
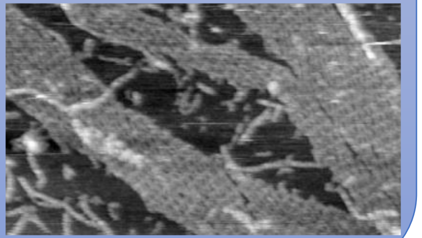


Figure from Schulman, Winfree, *PNAS* 2009

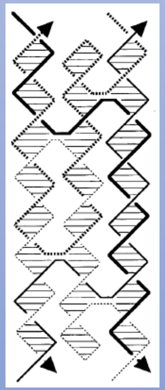
Practice of DNA tile self-assembly

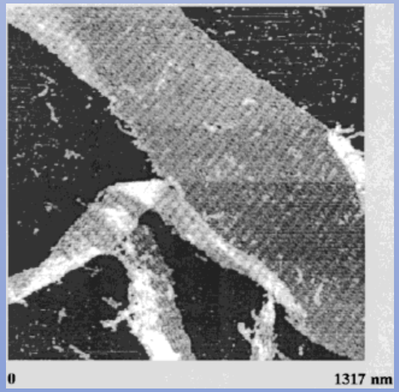
double-crossover tile (Winfree, Liu, Wenzler, Seeman, *Nature* 1998)



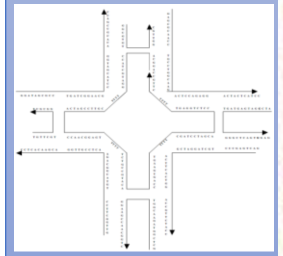


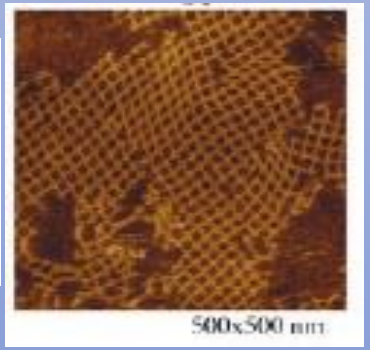
triple-crossover tile (LaBean, Yan, Kopatsch, Liu, Winfree, Reif, Seeman, *JACS* 2000)



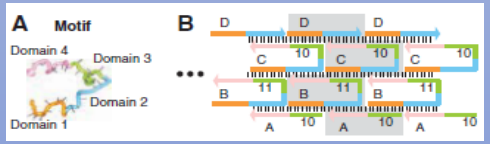


4x4 tile (Yan, Park, Finkelstein, Reif, LaBean, *Science* 2003)



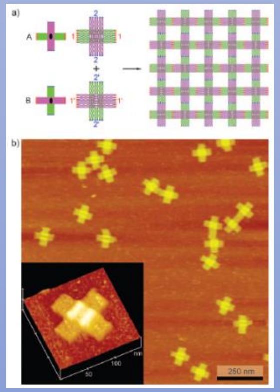


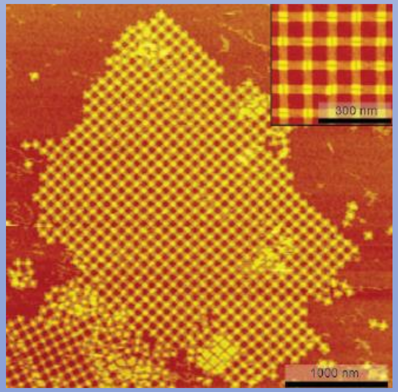
single-stranded tile (Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif, *Science* 2008)



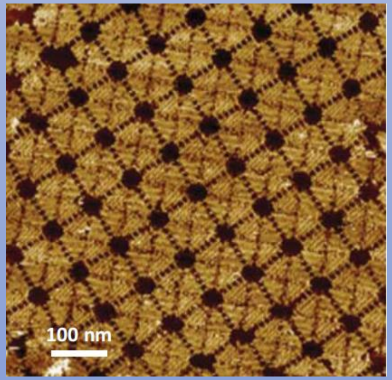
150 nm

DNA origami tile (Liu, Zhong, Wang, Seeman, *Angewandte Chemie* 2011)





Tikhomirov, Petersen, Qian, *Nature Nanotechnology* 2017

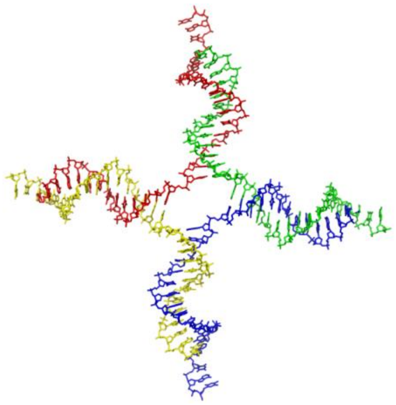


Theory of *algorithmic* self-assembly

What if…
… there is more than one tile type?
… some sticky ends are “weak”?

Erik Winfree

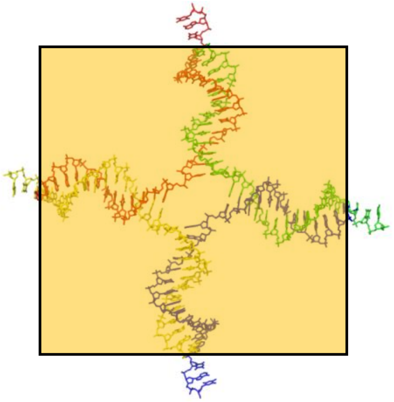
abstract Tile Assembly Model (aTAM)



Erik Winfree, Ph.D. thesis,
Caltech 1998

abstract Tile Assembly Model (aTAM)

- **tile type** = unit square



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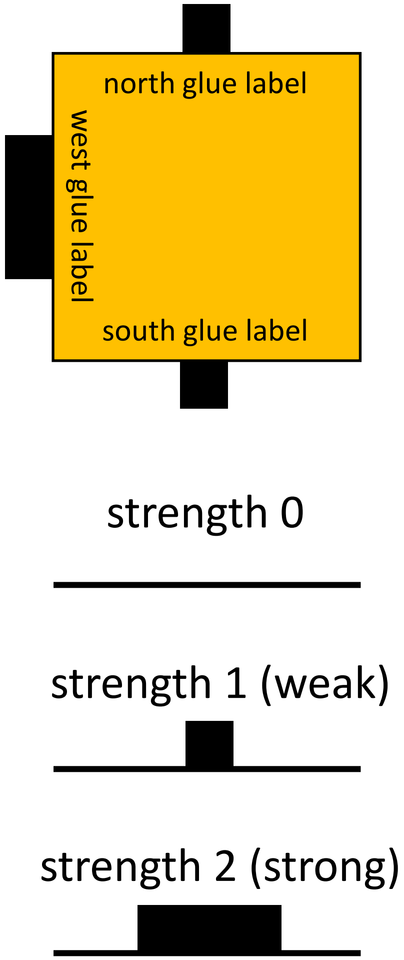
- each side has a **glue** with a **label** and **strength** (0, 1, or 2)



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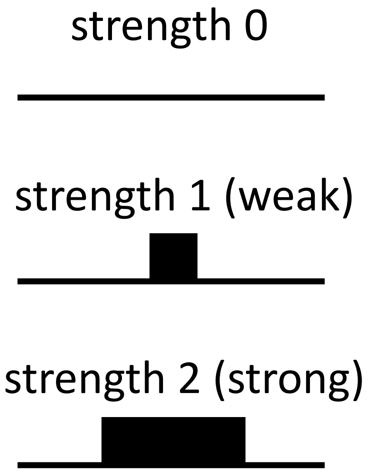
abstract Tile Assembly Model (aTAM)

- **tile type** = unit square
- each side has a **glue** with a **label** and **strength** (0, 1, or 2)
- tiles cannot rotate



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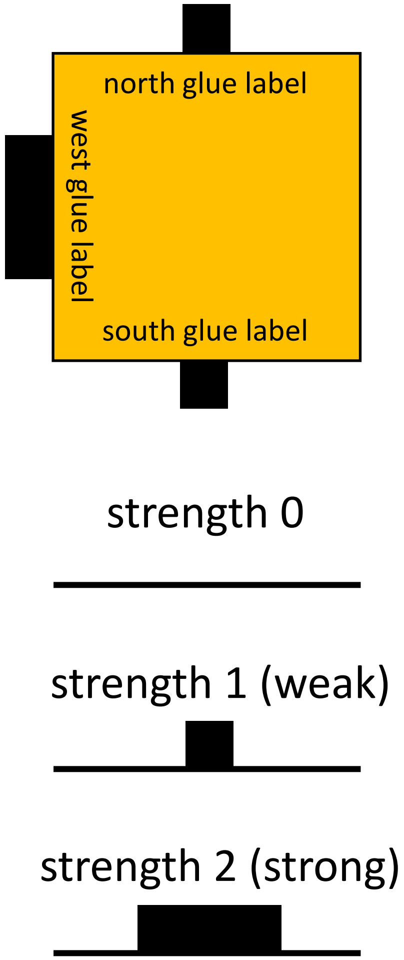

- finitely many tile **types**

- infinitely many **tiles**: copies of each type

Erik Winfree, Ph.D. thesis, Caltech 1998

abstract Tile Assembly Model (aTAM)

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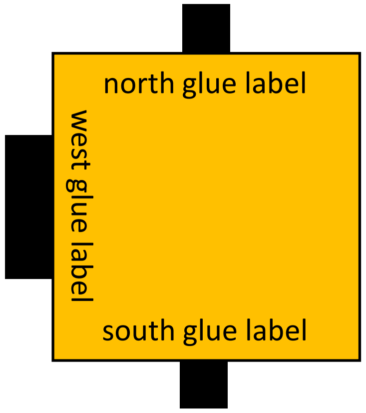

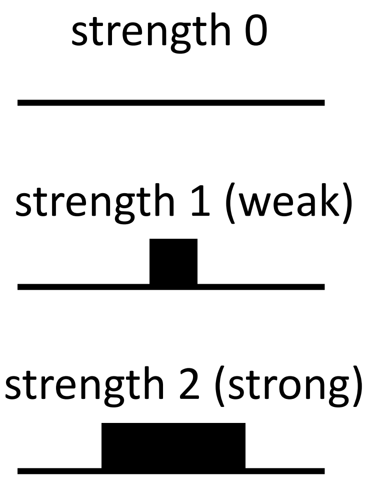

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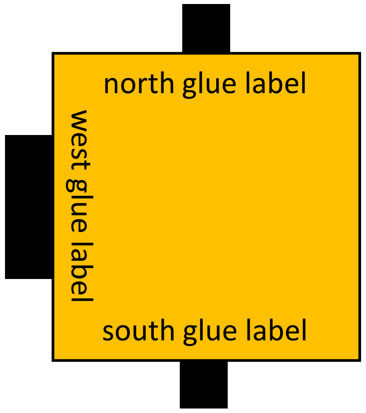

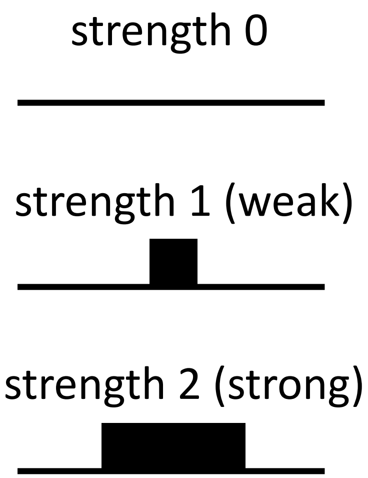

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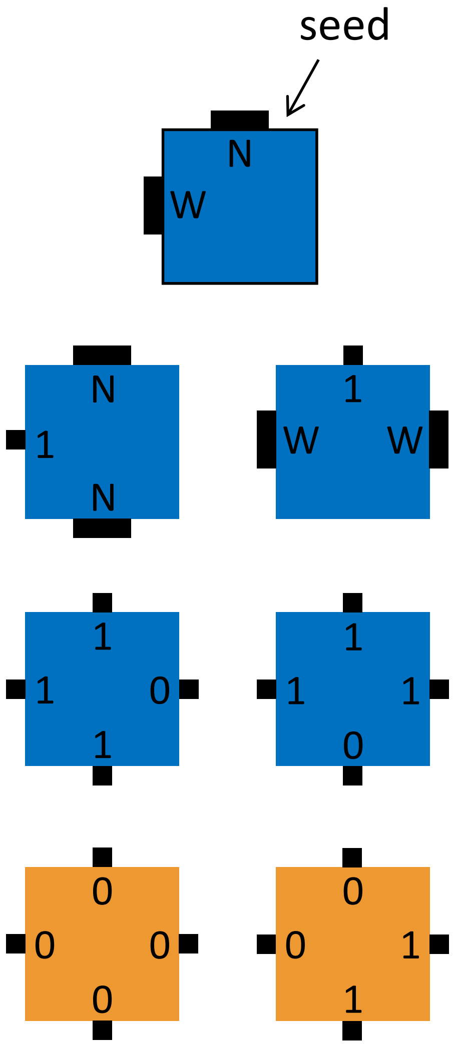
Erik Winfree, Ph.D. thesis, Caltech 1998

Example tile set



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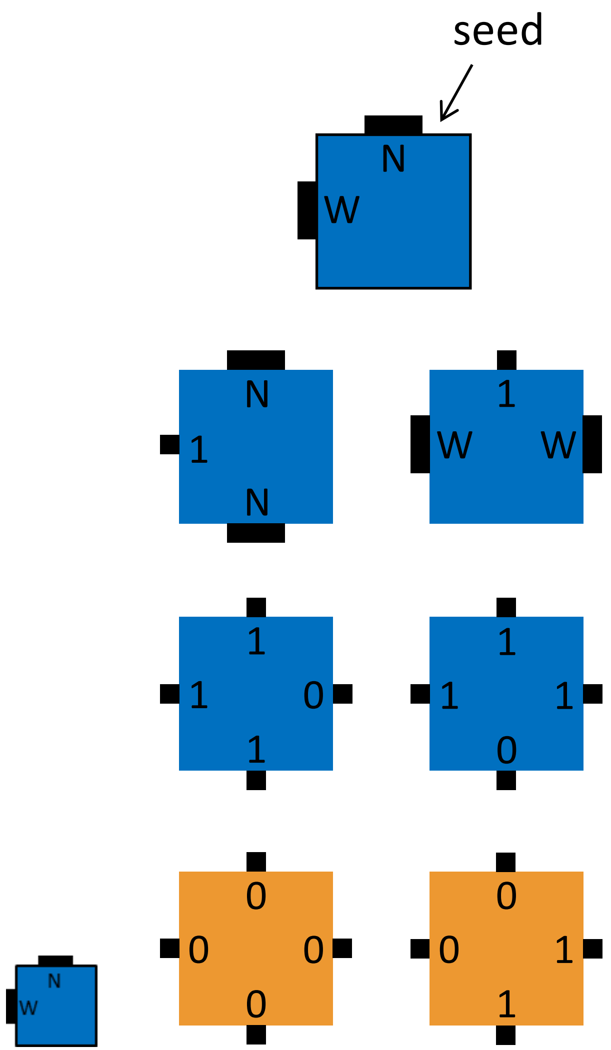

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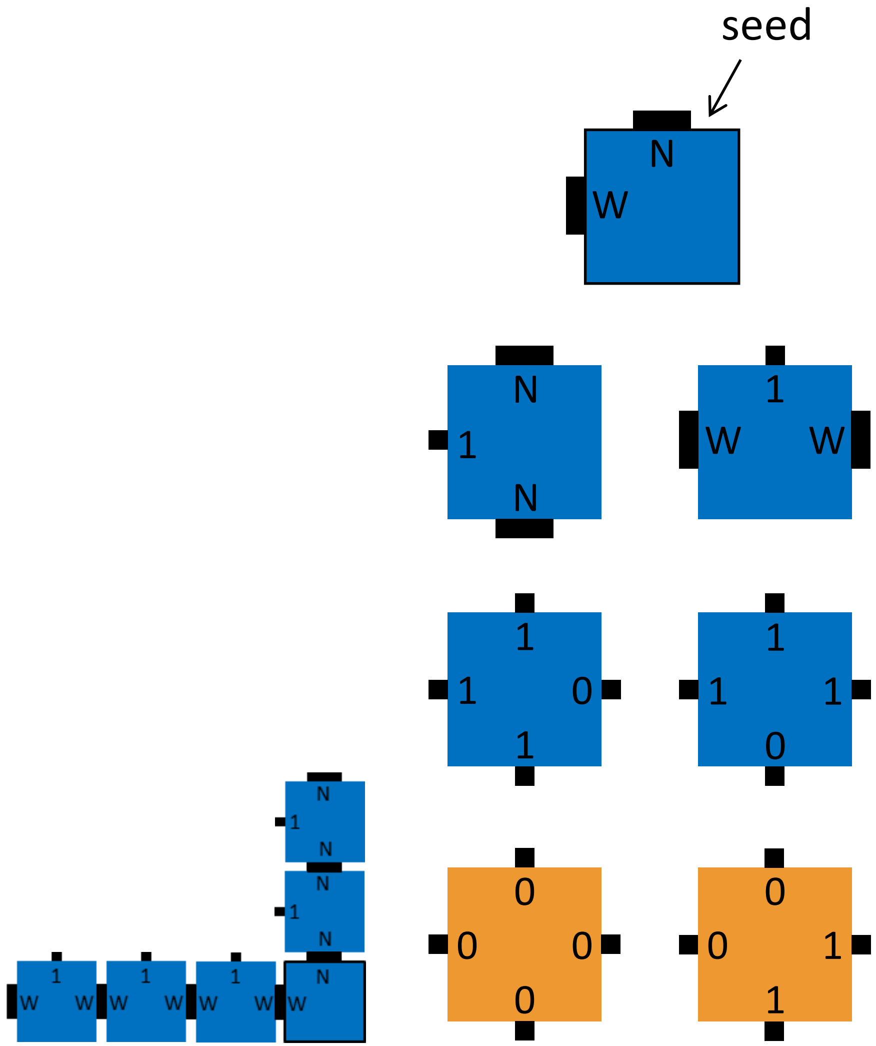

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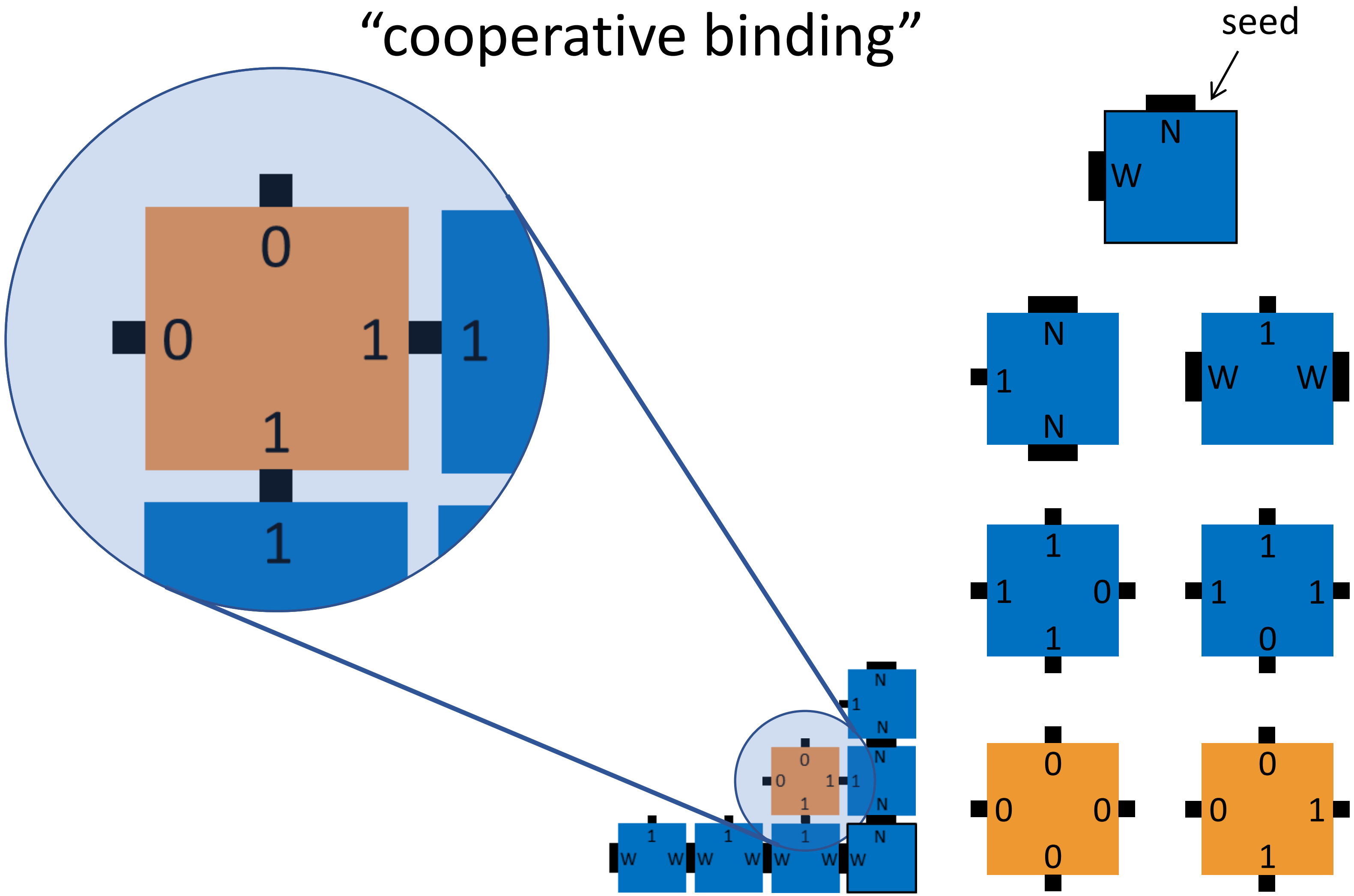

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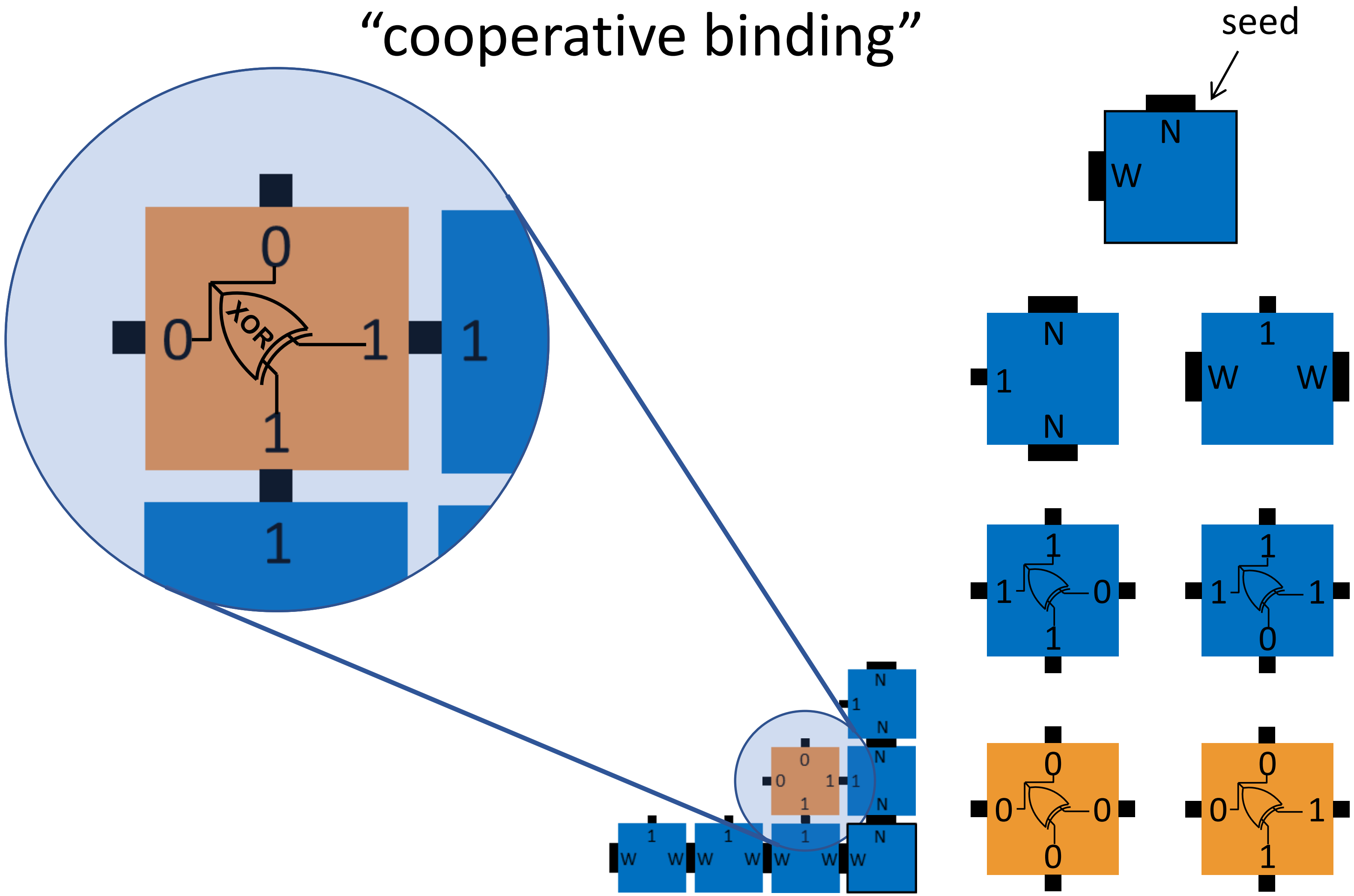

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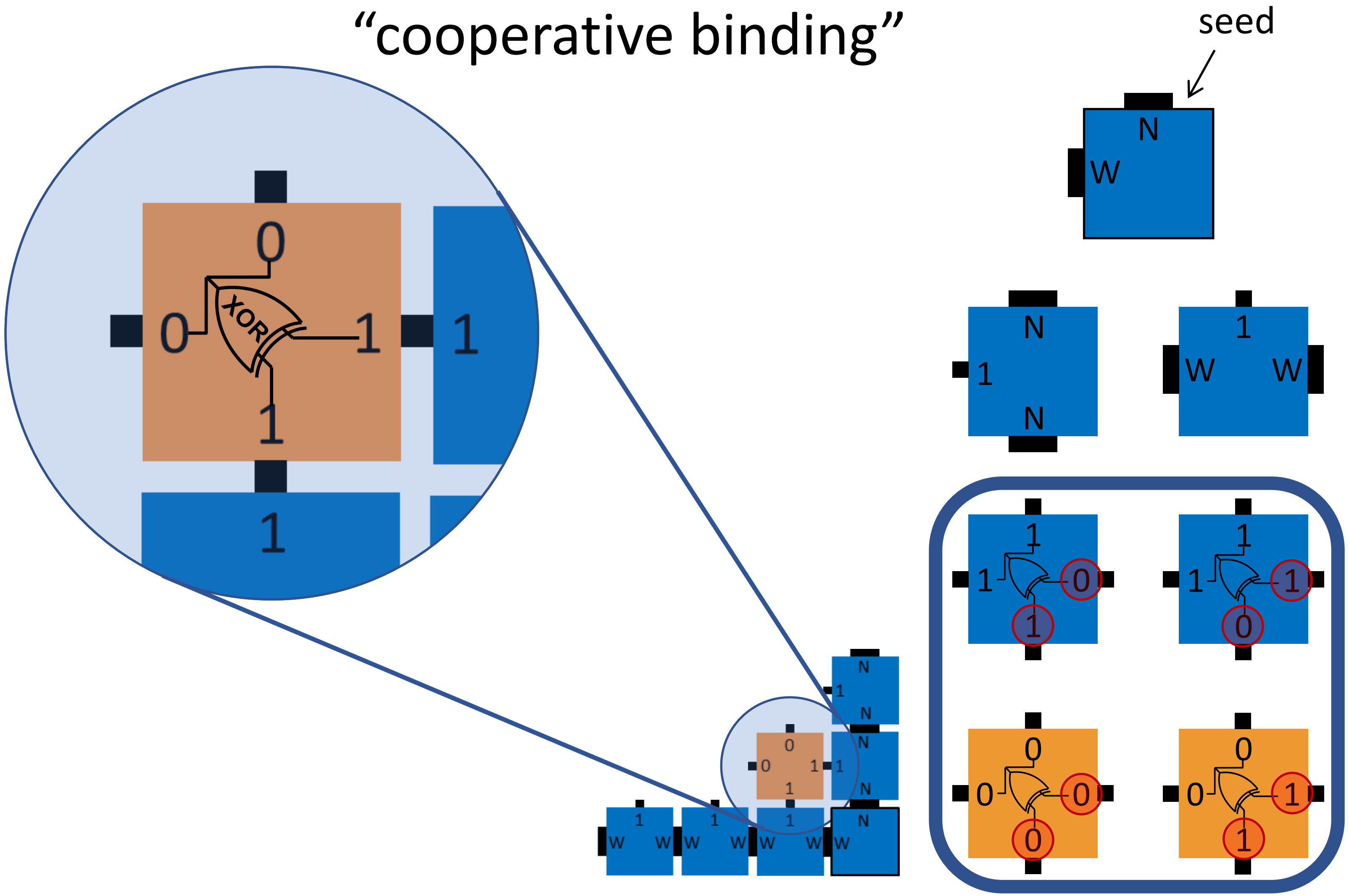
“cooperative binding”



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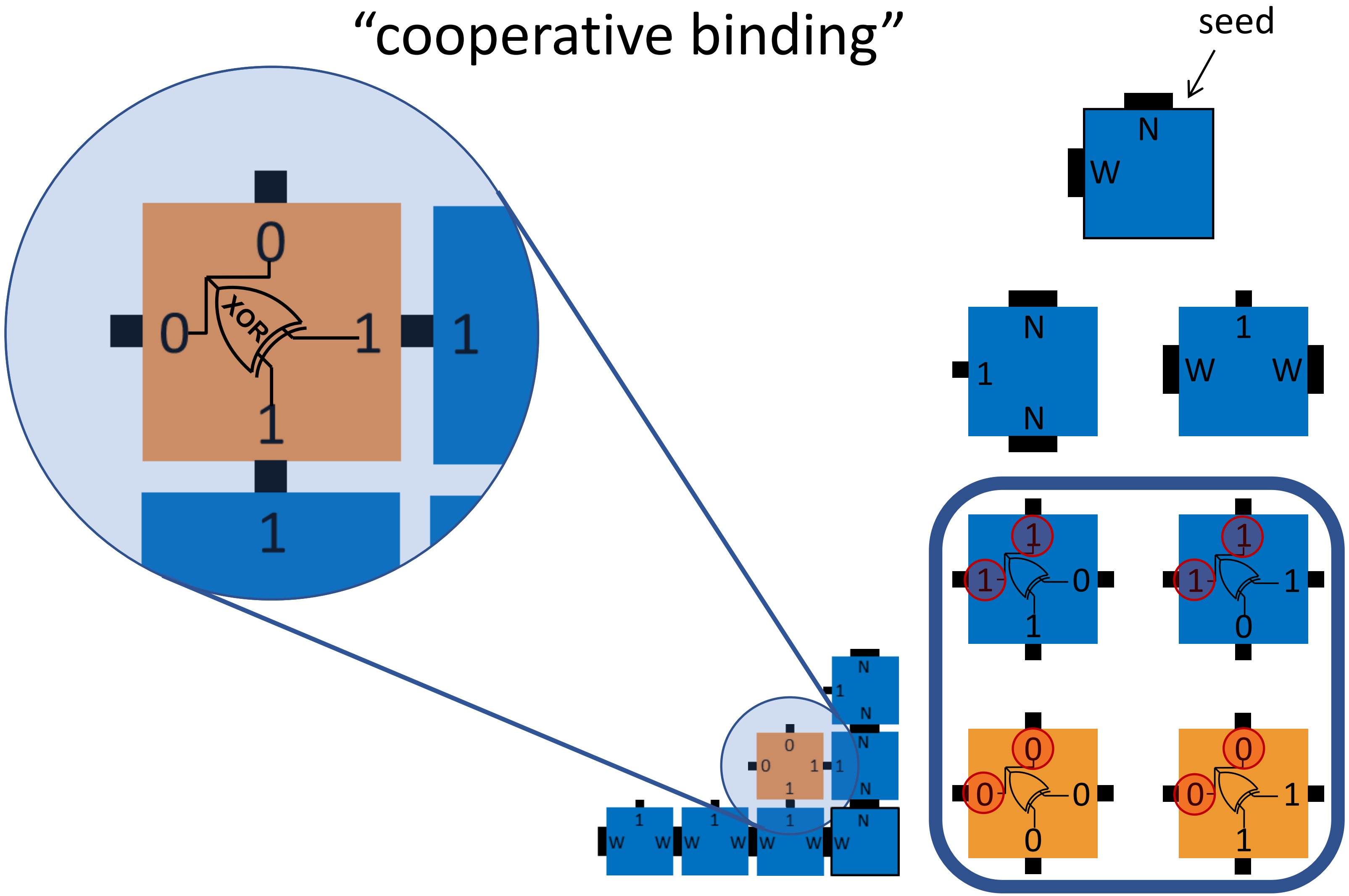

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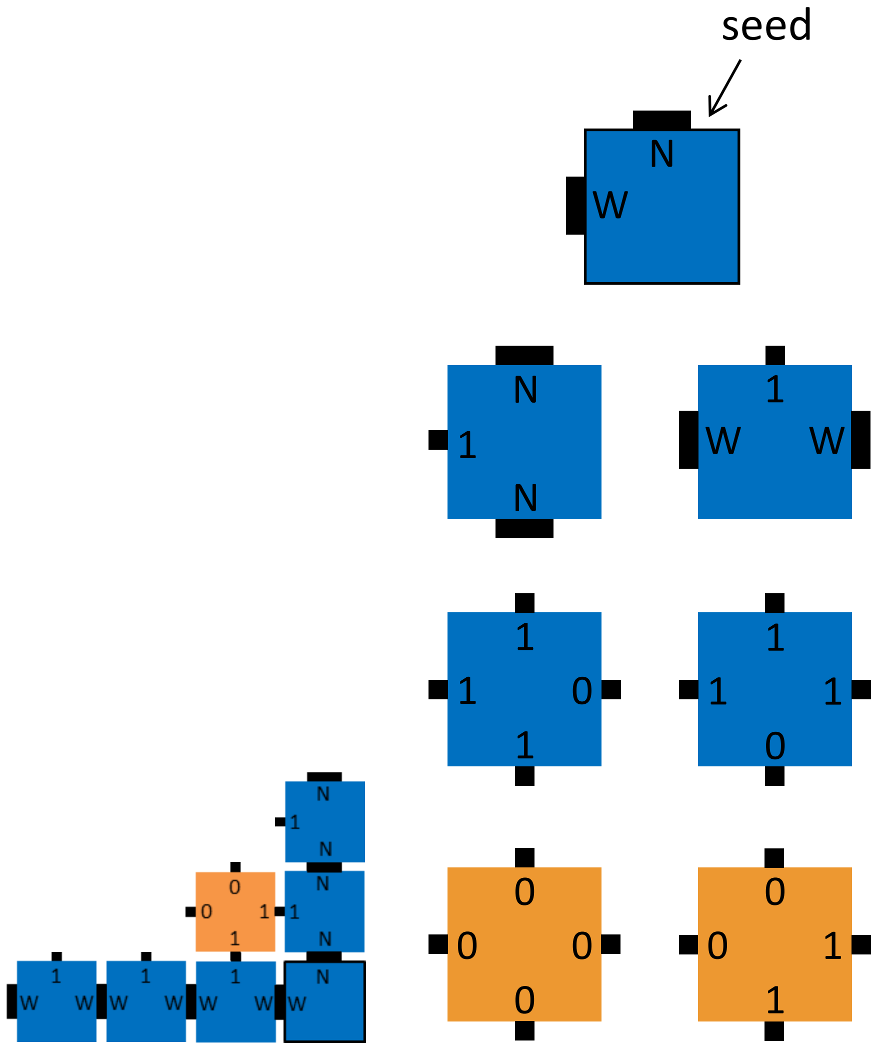
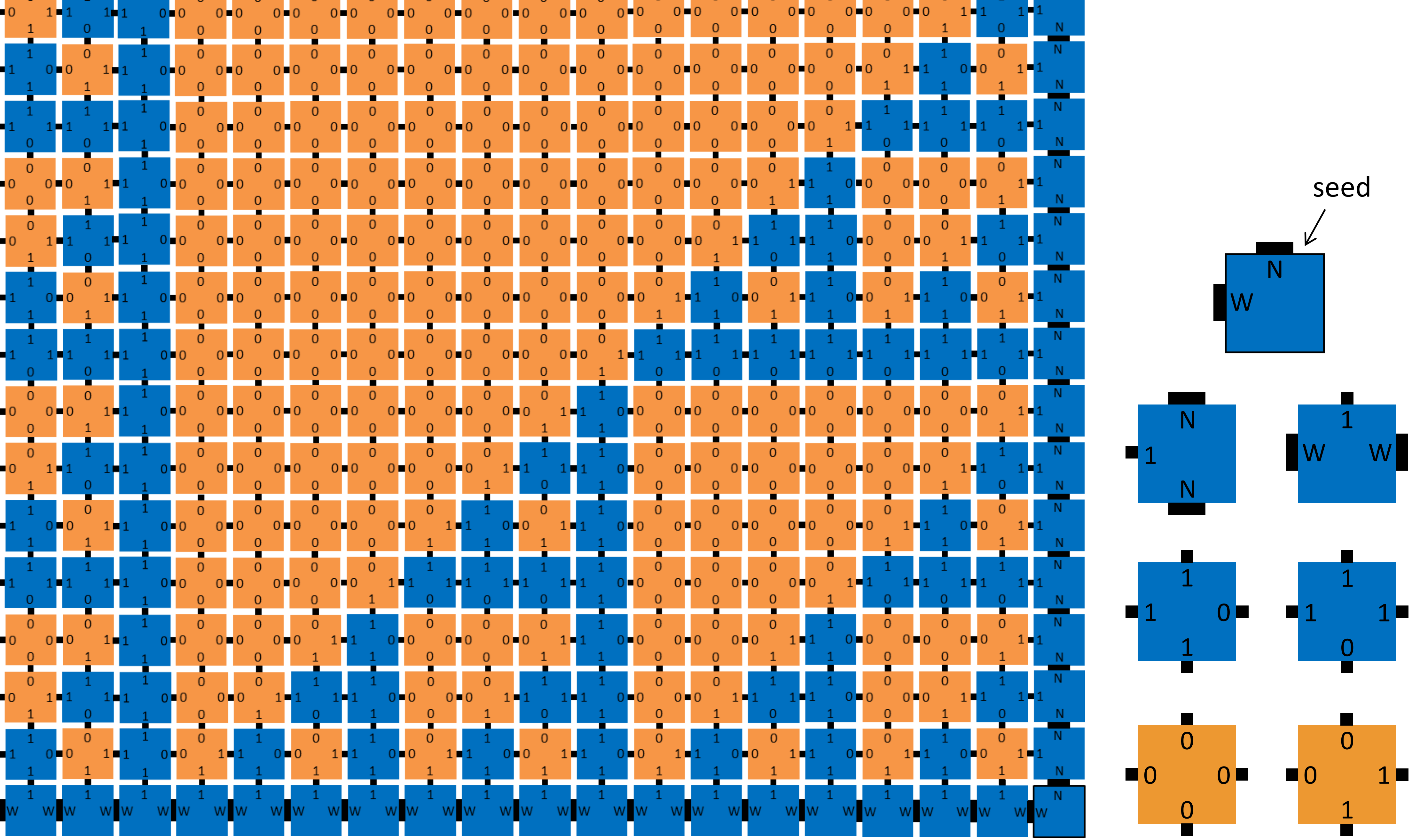
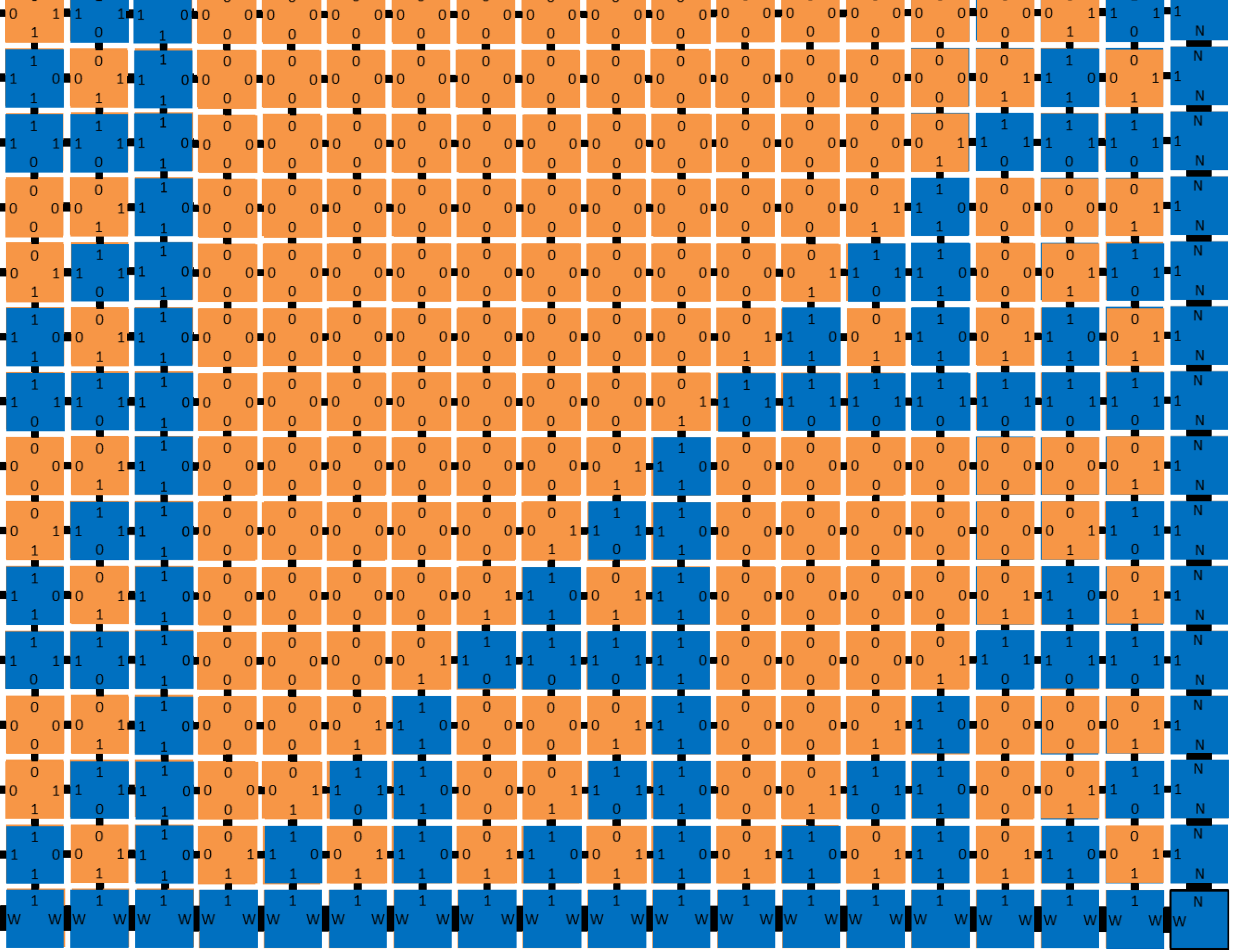
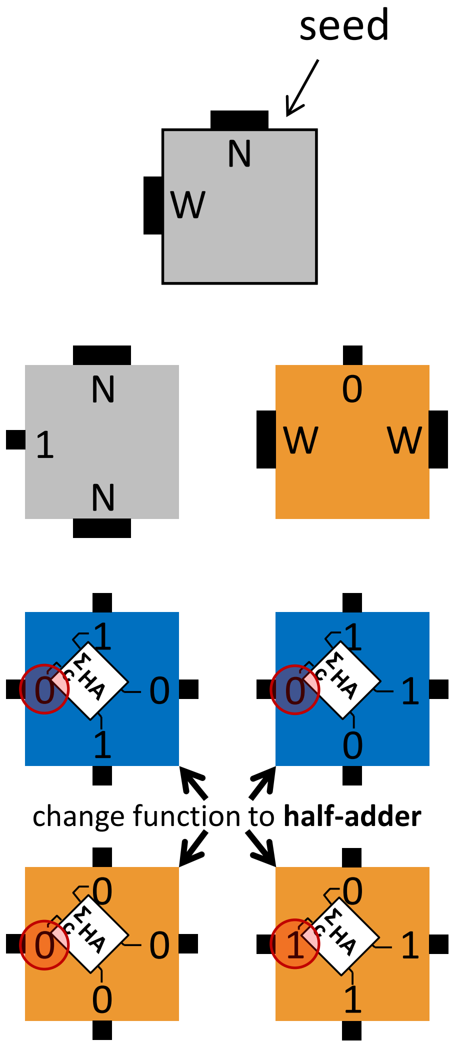
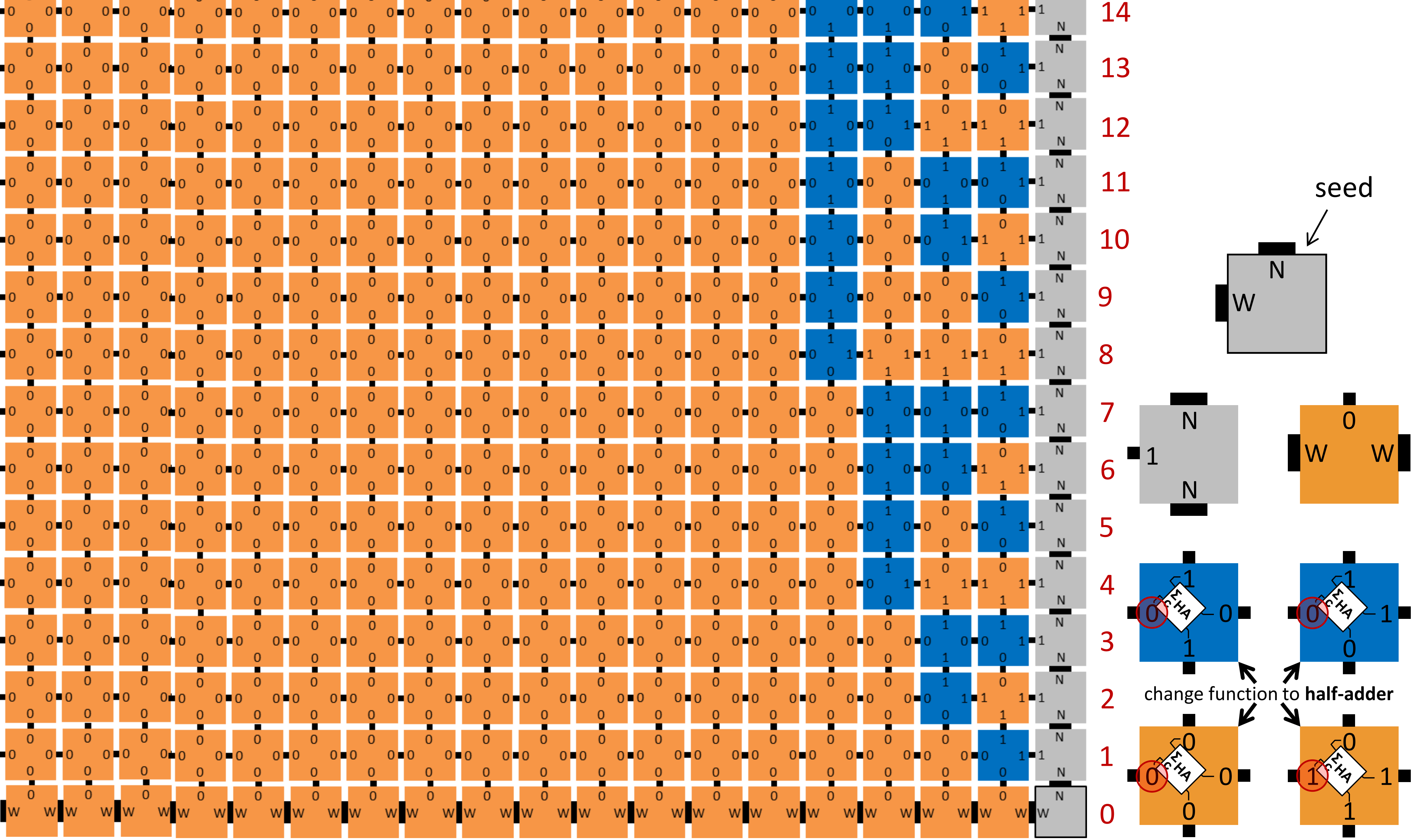



seed




seed
N
W
N
1
N
0
W
W
change function to half-adder


14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
seed
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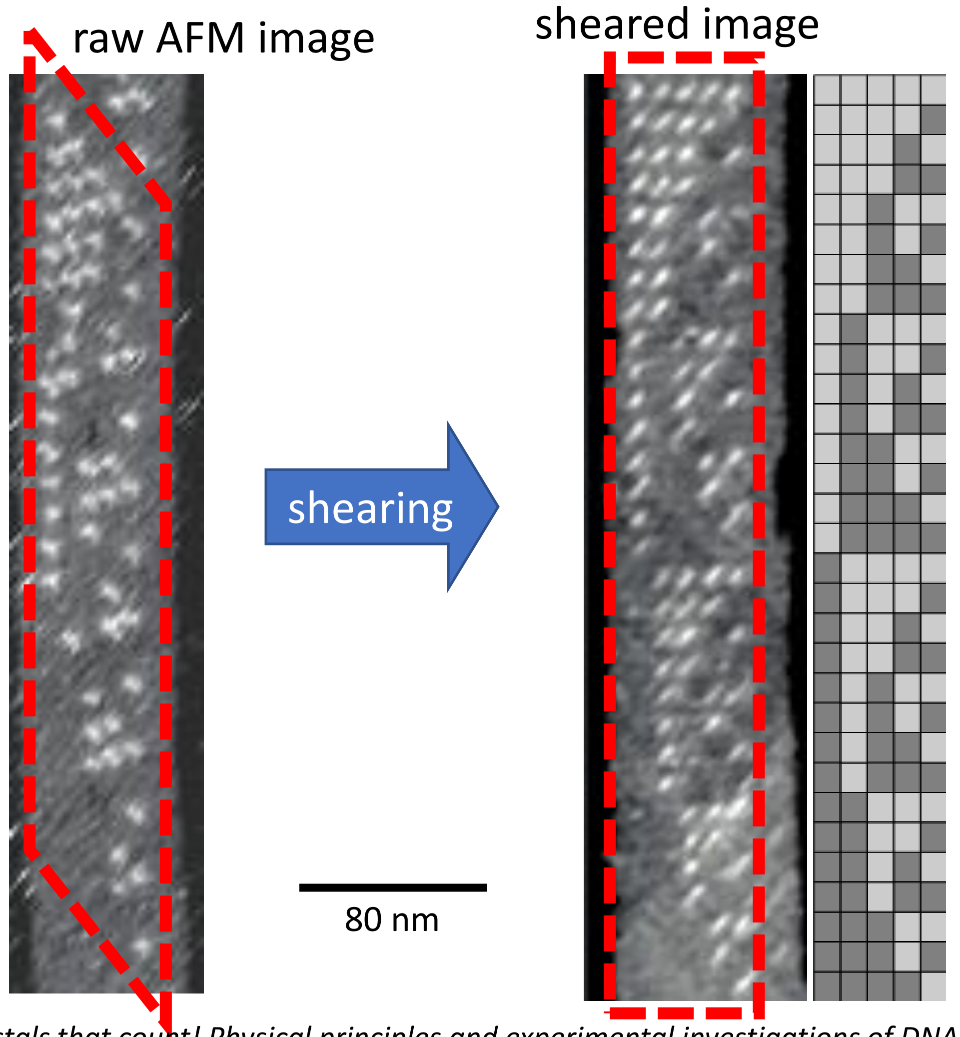
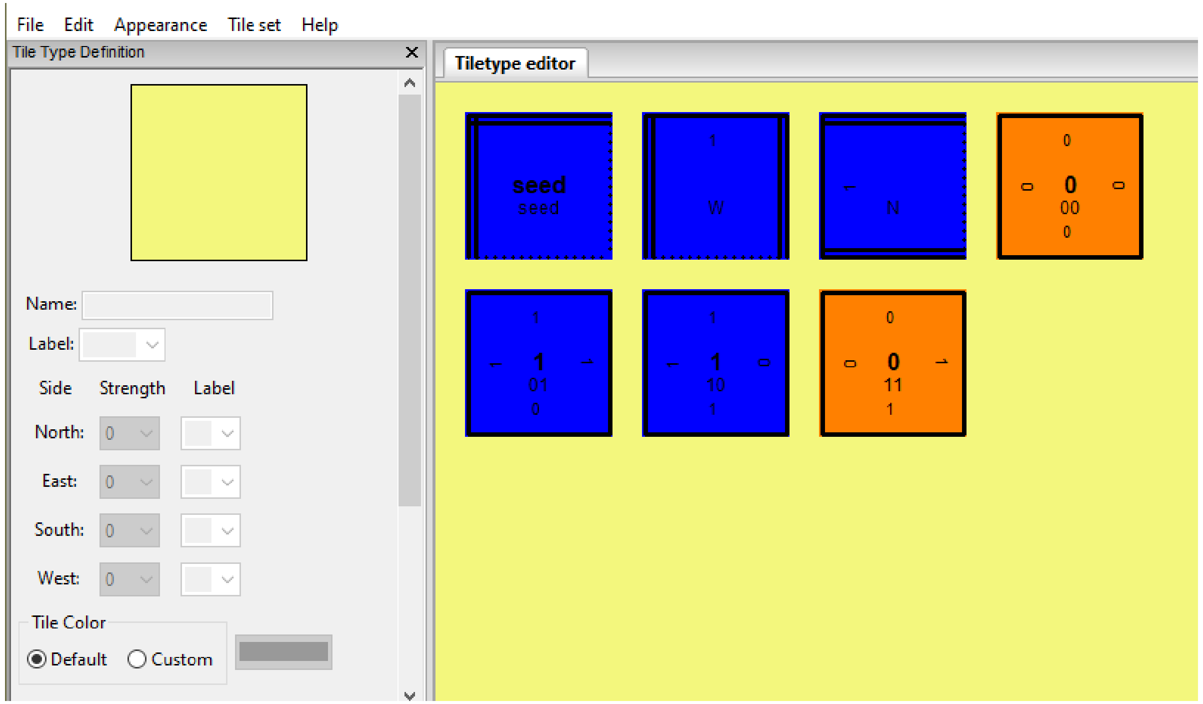
Algorithmic self-assembly in action

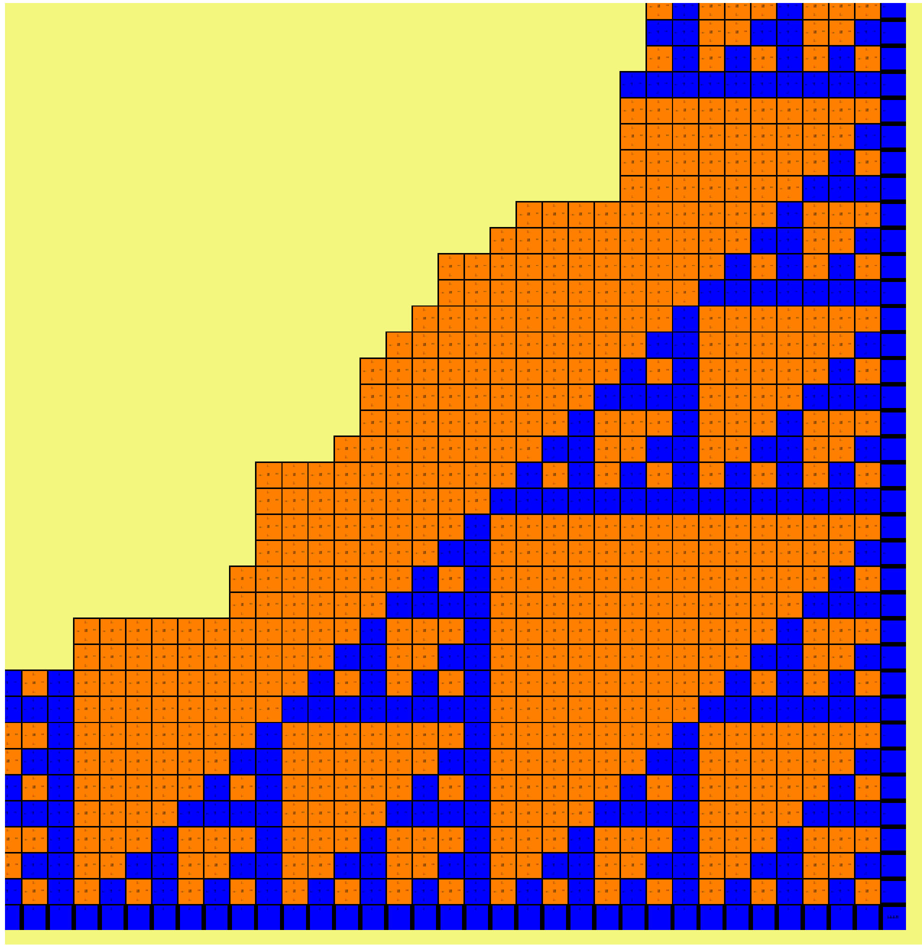


[*Crystals that count! Physical principles and experimental investigations of DNA tile self-assembly*, Constantine Evans, Ph.D. thesis, Caltech, 2014]

aTAM simulator (ISU TAS by Matt Patitz)

http://self-assembly.net/wiki/index.php?title=ISU_TAS
http://self-assembly.net/wiki/index.php?title=ISU_TAS_Tutorials
See also WebTAS by the same group:
http://self-assembly.net/software/WebTAS/WebTAS-latest/





VersaTile (by Eric Martinez and Cameron Chalk) https://github.com/ericmichael/polyomino
and xgrow (by Erik Winfree) https://www.dna.caltech.edu/Xgrow/

Tile complexity of squares

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- [*Note: we have not formally defined the aTAM yet… first let’s build intuition.*]

The program size complexity of self-assembled squares

Question: How many tile types do we need to self-assemble an *n* x *n* square?

https://www.dna.caltech.edu/Papers/squares_STOC.pdf
This paper is directly responsible for convincing many theoretical computer scientists that DNA self-assembly is worth studying.

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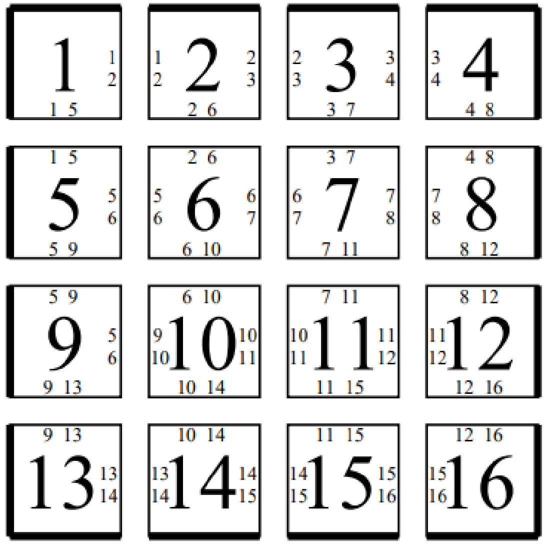

All glues are strength 2
(alternately: all are strength 1 and *temperature* $\tau = 1$)

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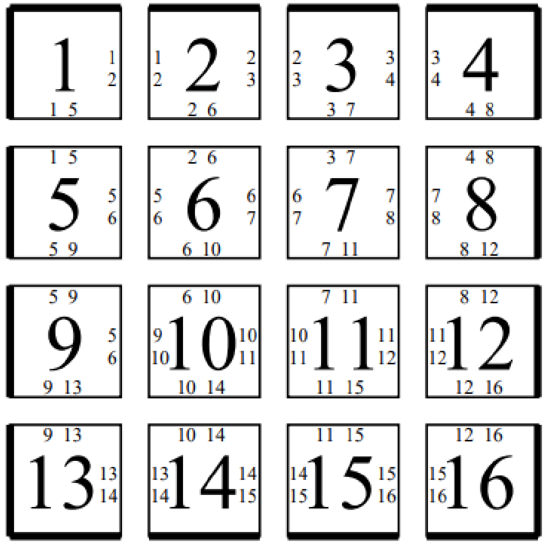

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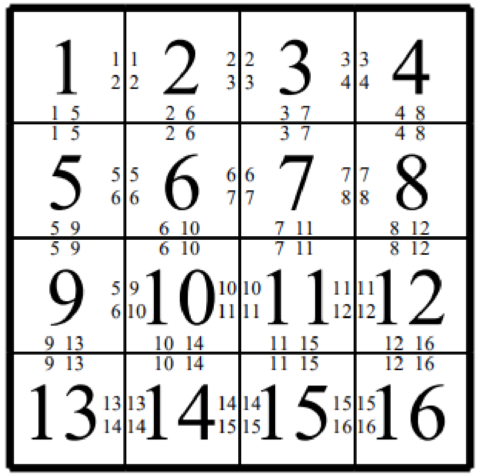

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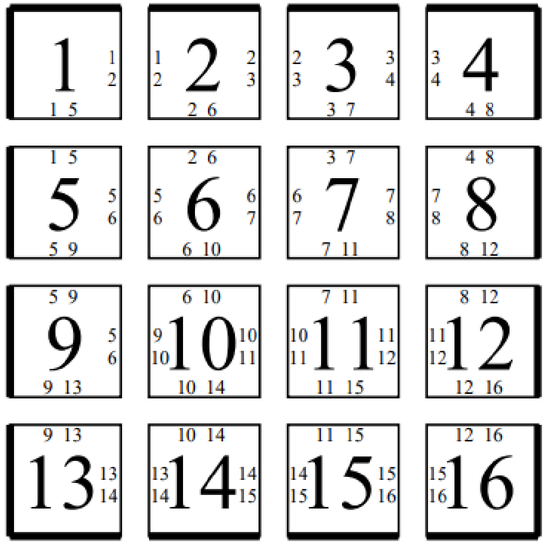

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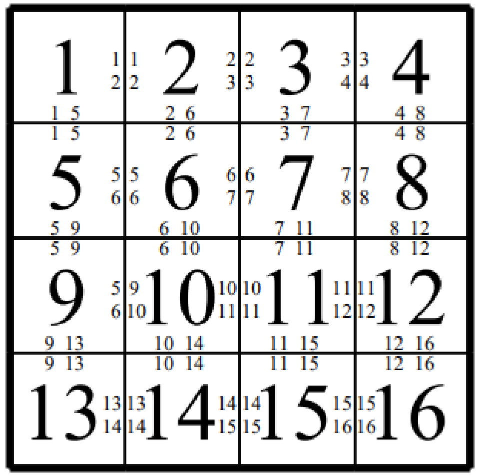

How many tile types does this construction need in general to assemble an *n* x *n* square?

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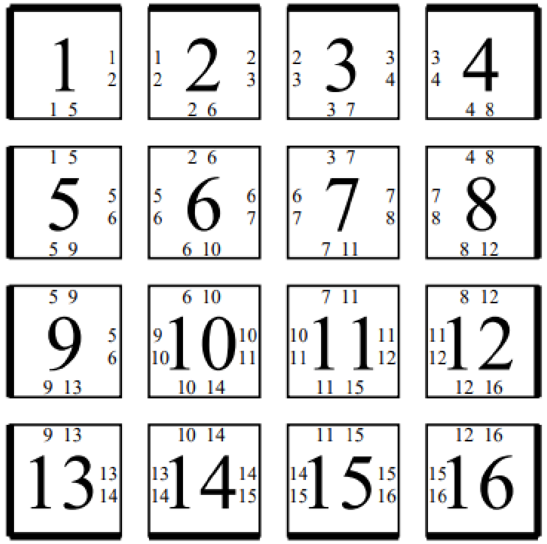

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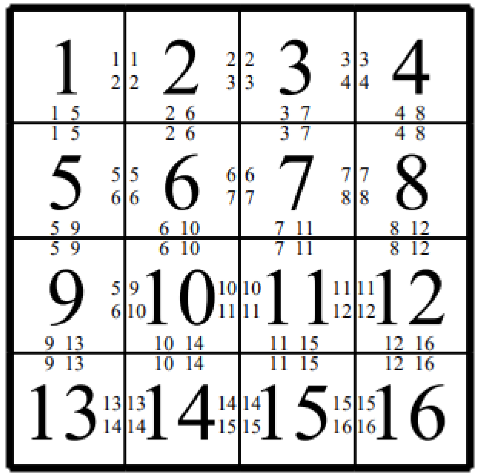

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Tile complexity at temperature $\tau = 1$ (i.e., no cooperative binding allowed)

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Can we do better?

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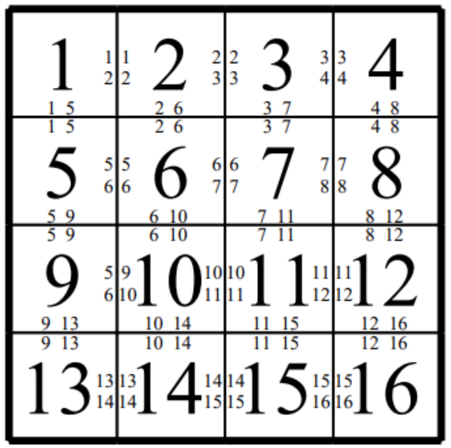

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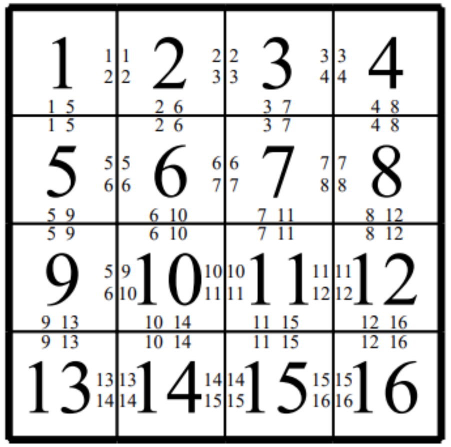

Theorem: At temperature $\tau = 1$, if all pairs of adjacent tiles bind with positive strength, then for every positive integer n, n^2 tile types are <u>necessary</u> to self-assemble an n x n square.

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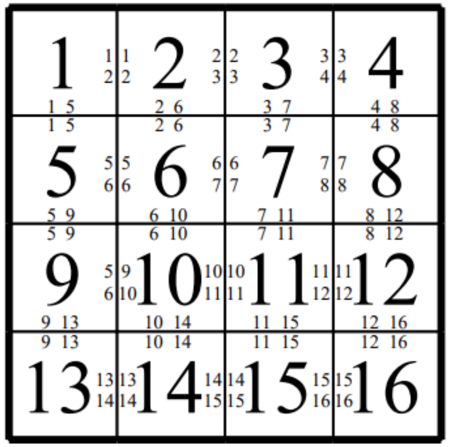
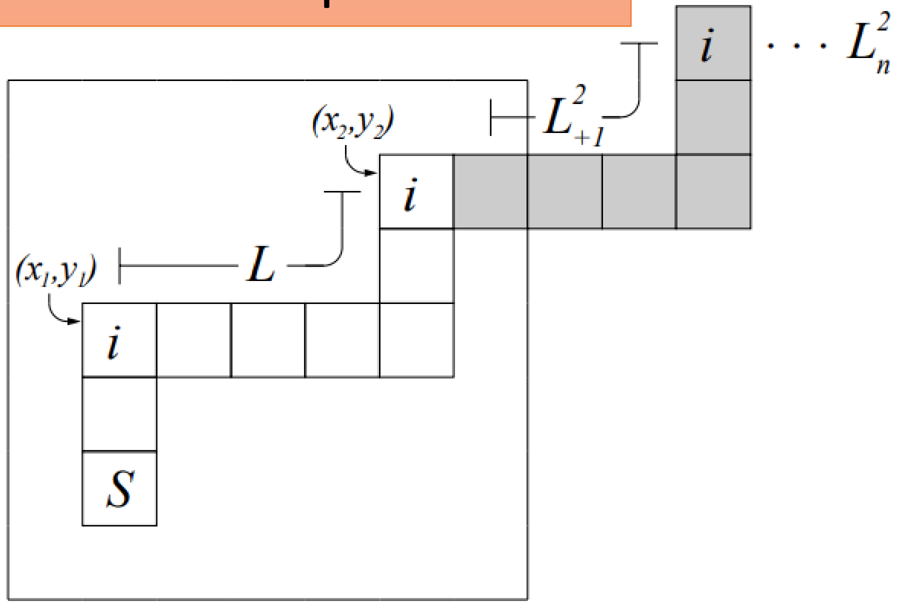


Proof: Suppose for contradiction we use the same tile type i at positions (x_1,y_1) and (x_2,y_2). Then they have a path L between them with all positive-strength glues, and this can happen instead:



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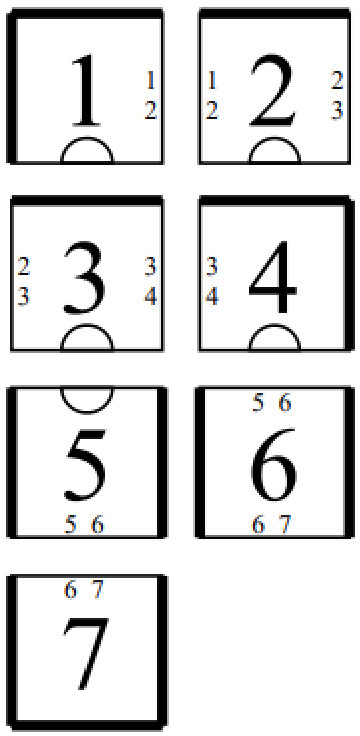

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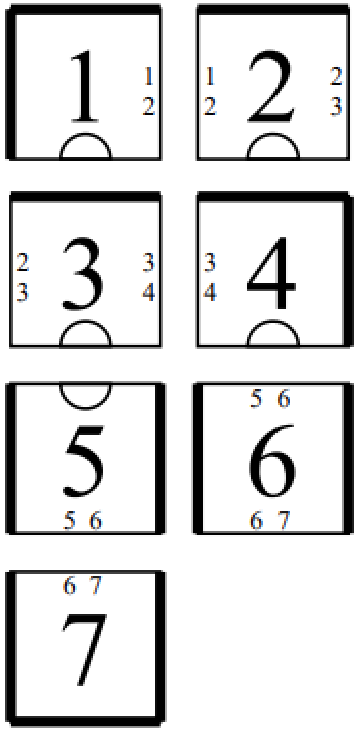

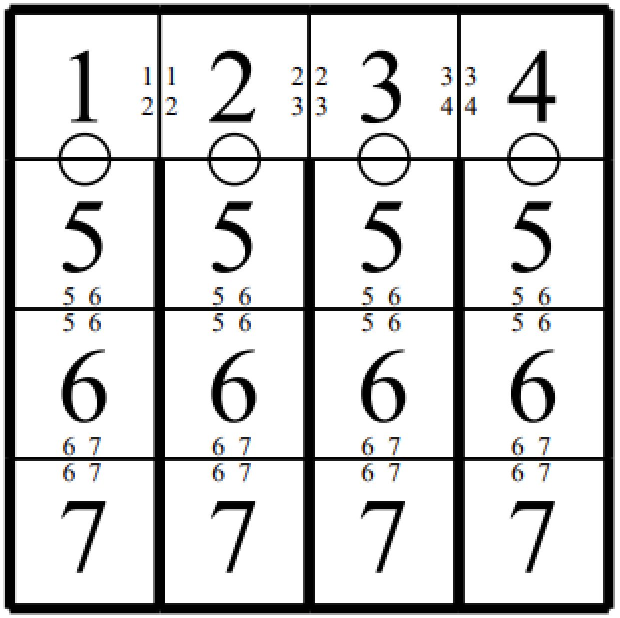

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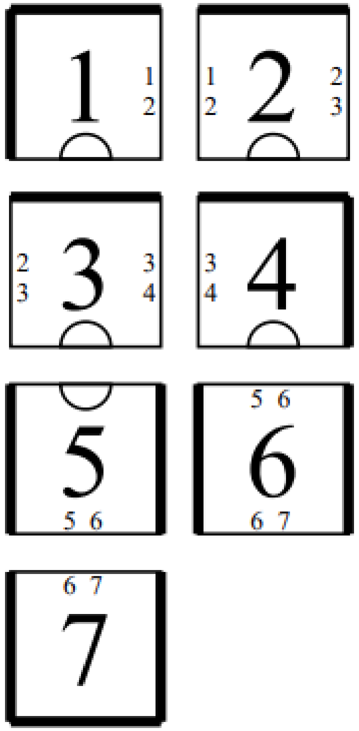

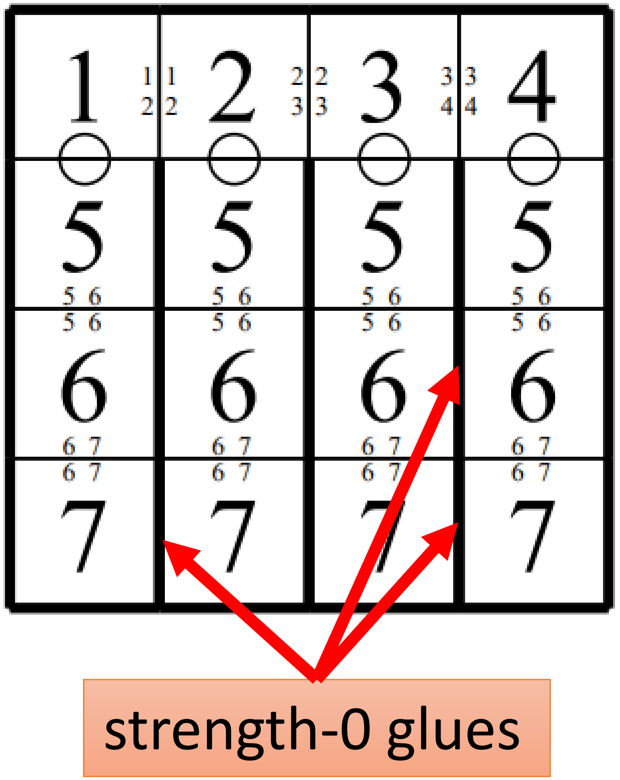

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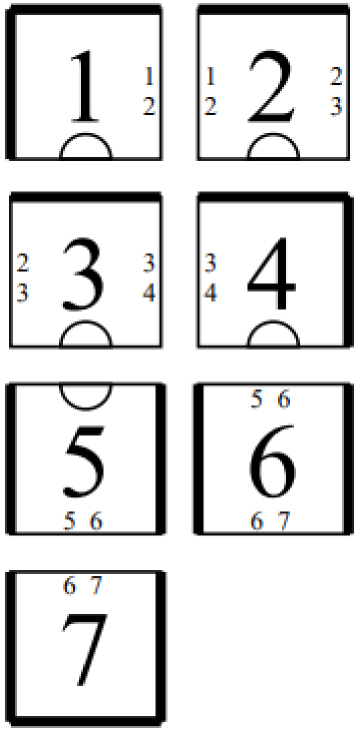

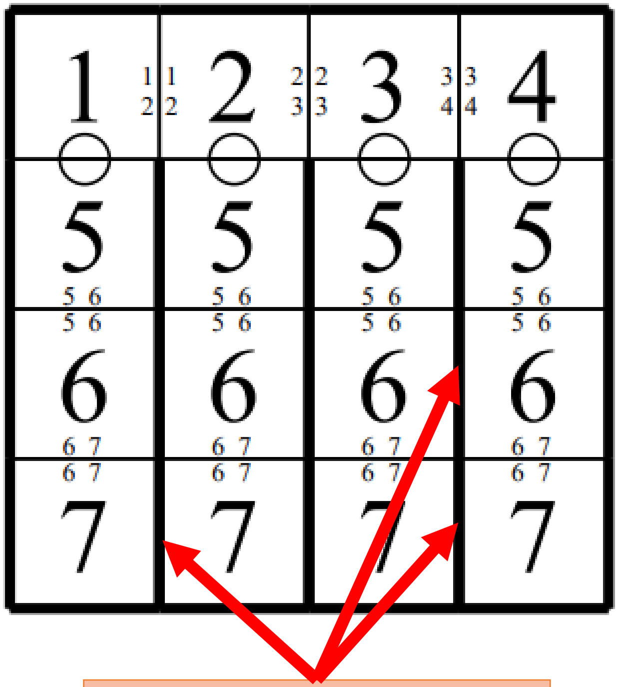

strength-0 glues

Tile complexity of this construction?

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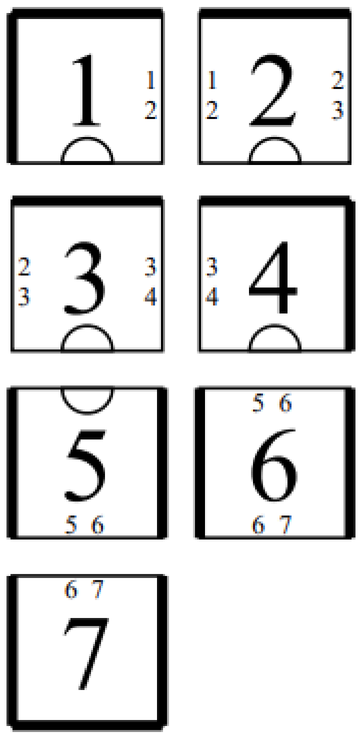

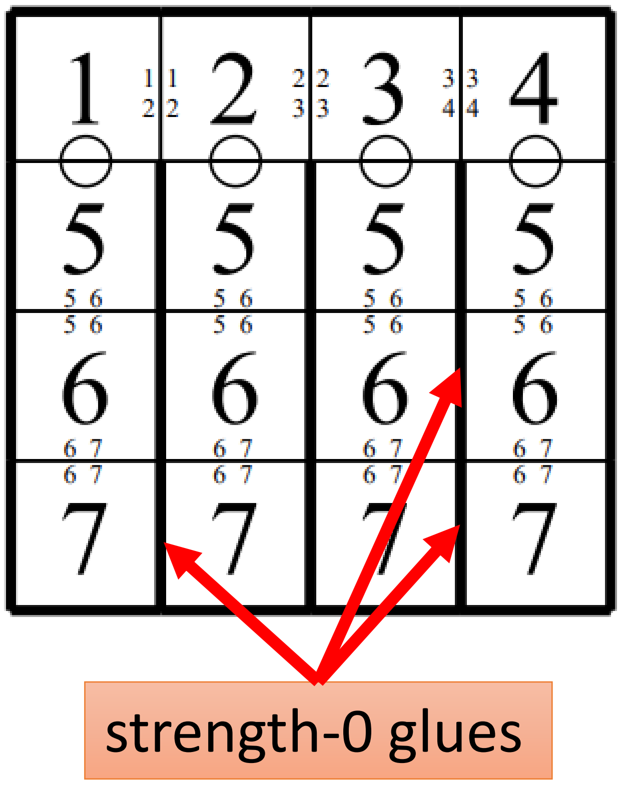

Tile complexity of this construction?

$2n - 1 = O(n)$

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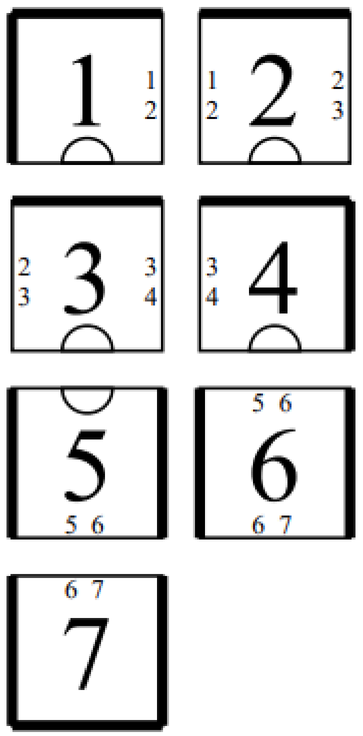

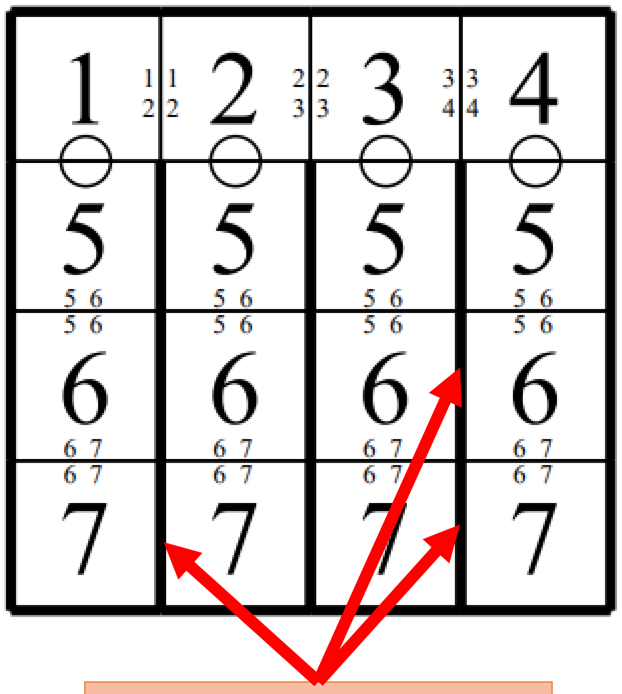

Tile complexity of this construction?

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Conjecture: The temperature $\tau = 1$ tile complexity of an n x n square is $\Omega(n)$.

(most recent progress:
https://arxiv.org/abs/1902.02253
https://arxiv.org/abs/2002.04012)

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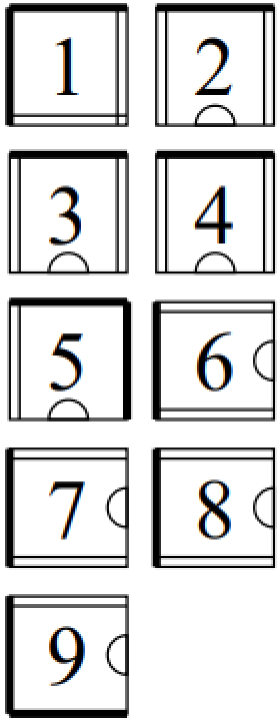

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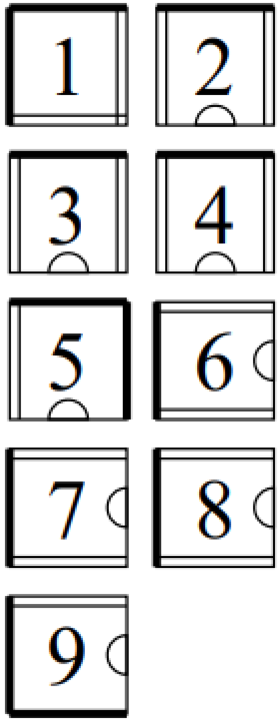

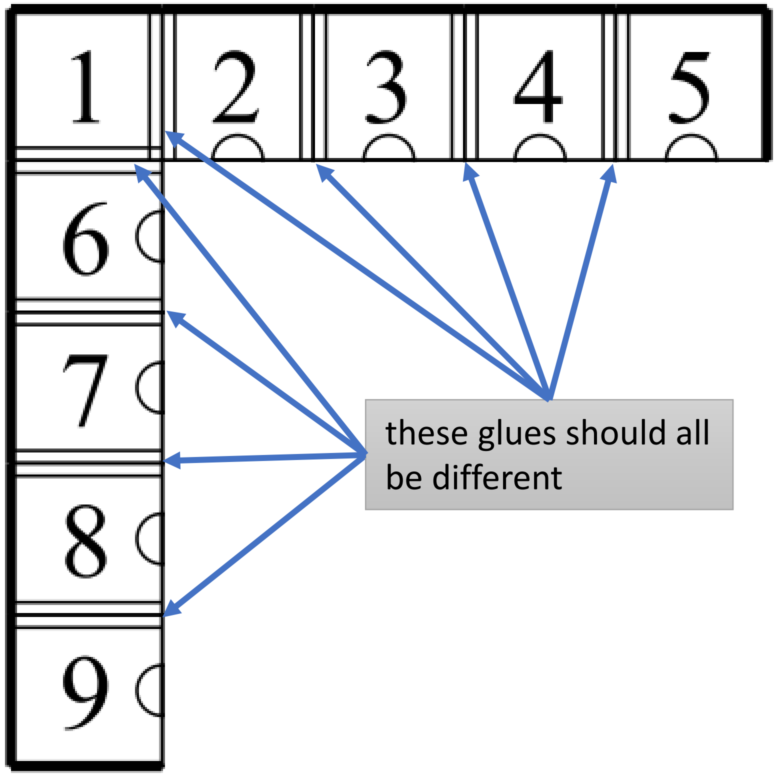

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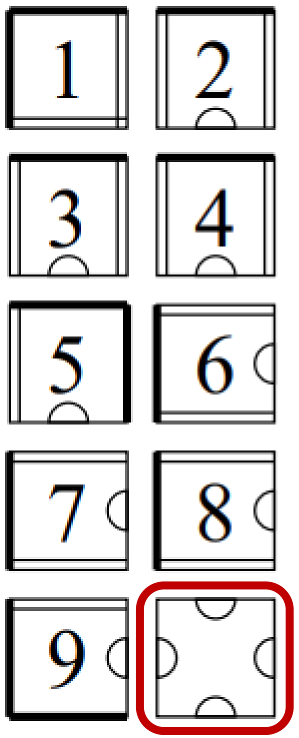
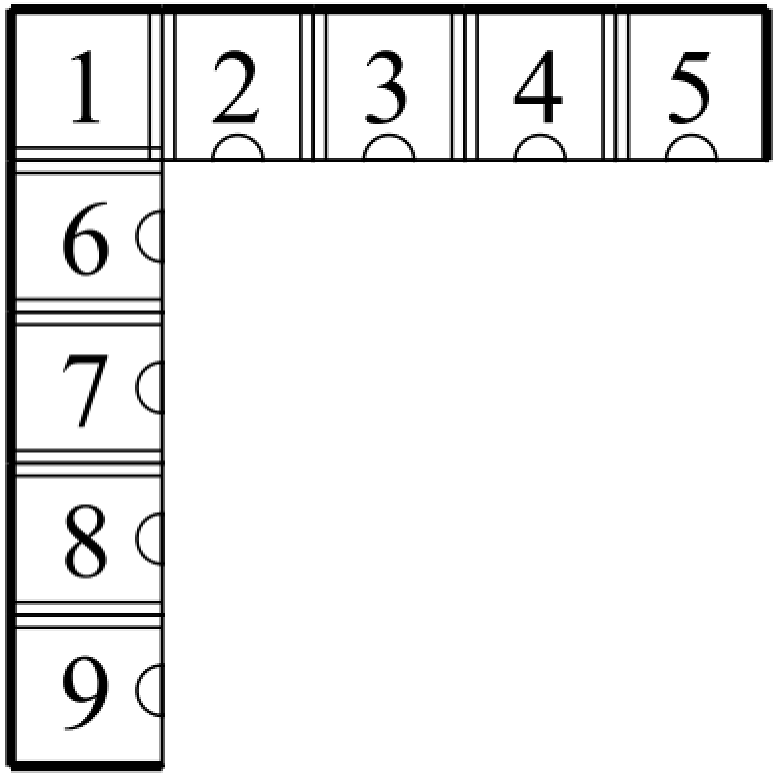
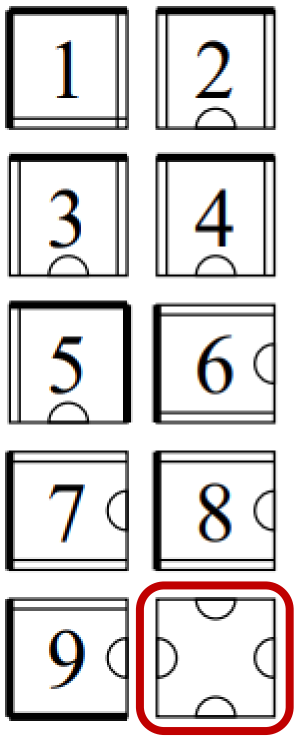
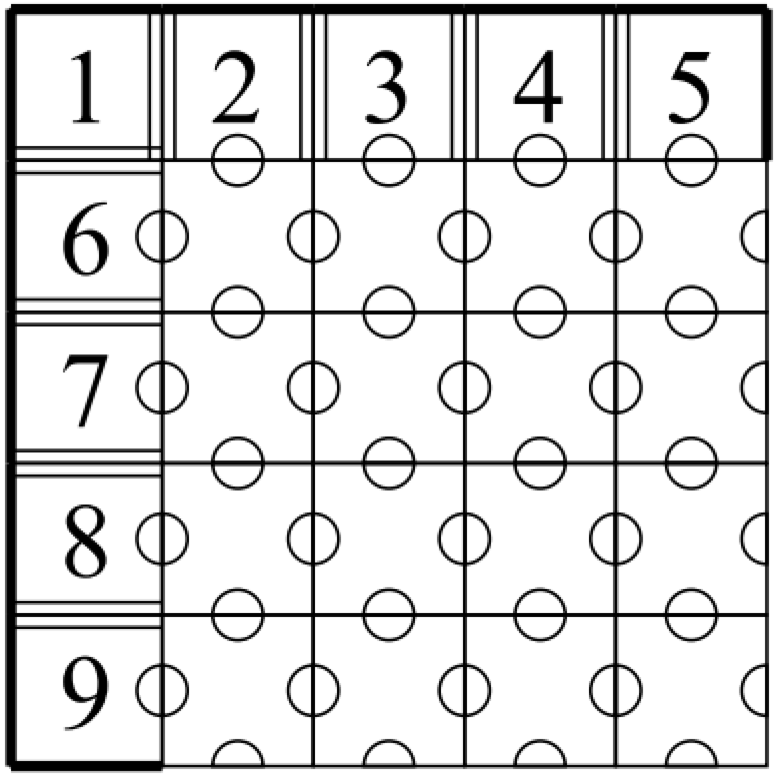


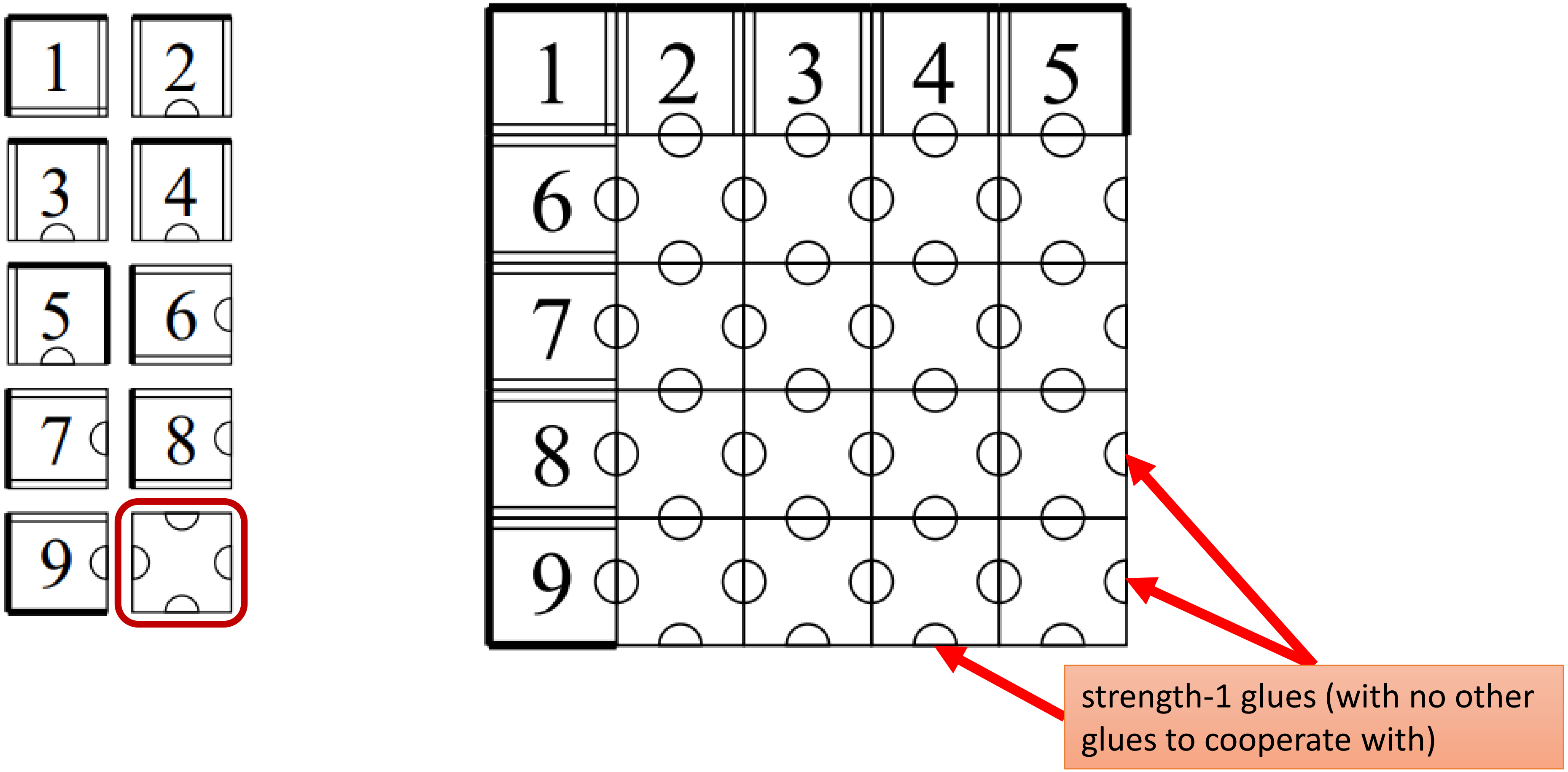


Tile complexity at temperature τ = 2 (i.e., cooperative binding allowed)

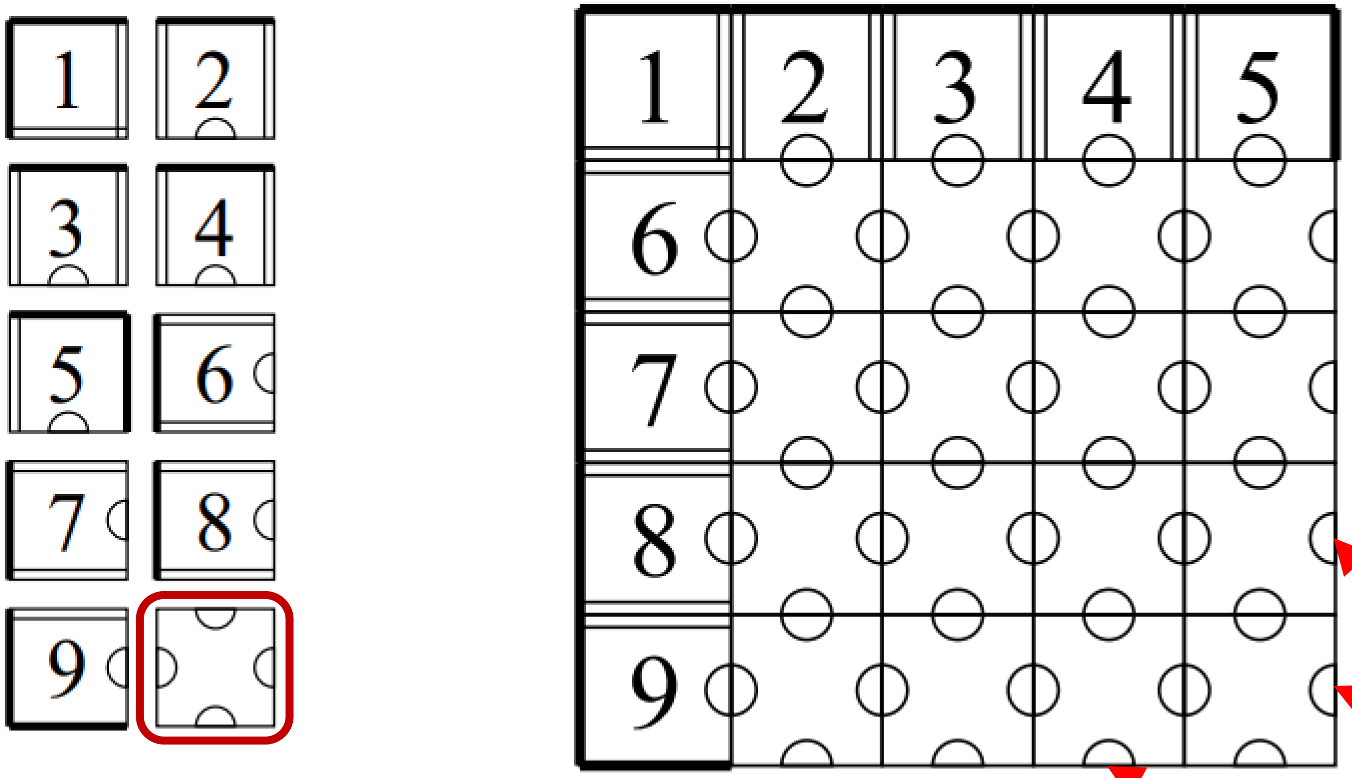




Tile complexity at temperature $\tau = 2$ (i.e., cooperative binding allowed)



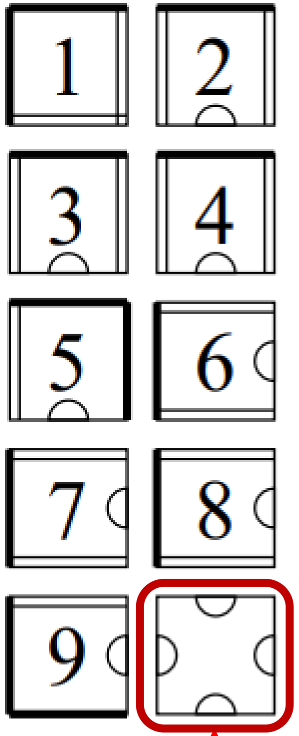
Tile complexity at temperature $\tau = 2$ (i.e., cooperative binding allowed)



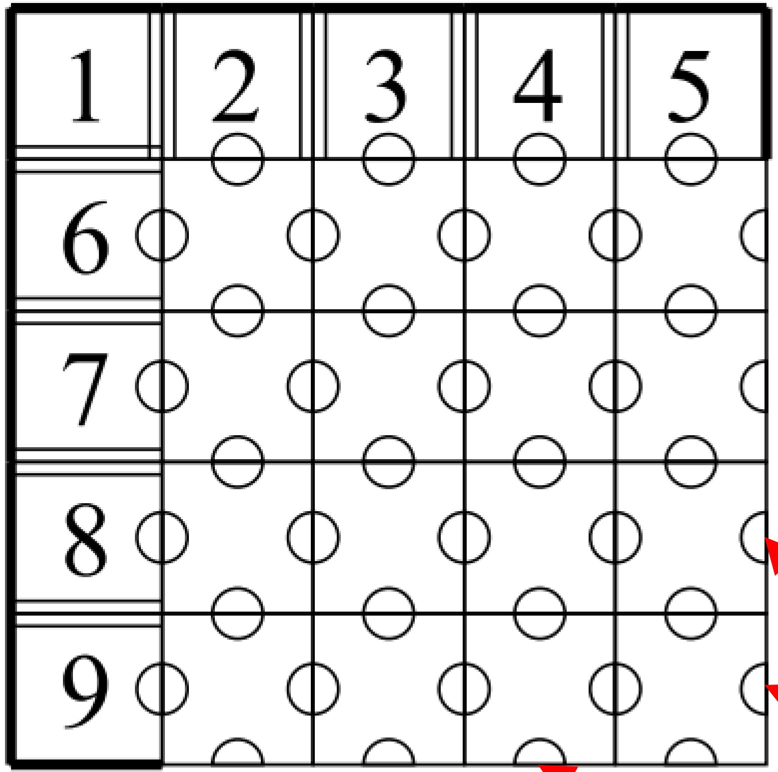
Tile complexity = $2n$

strength-1 glues (with no other glues to cooperate with)

Tile complexity at temperature $\tau = 2$ (i.e., cooperative binding allowed)



This tile completes an n x n “L shape” into an n x n square.

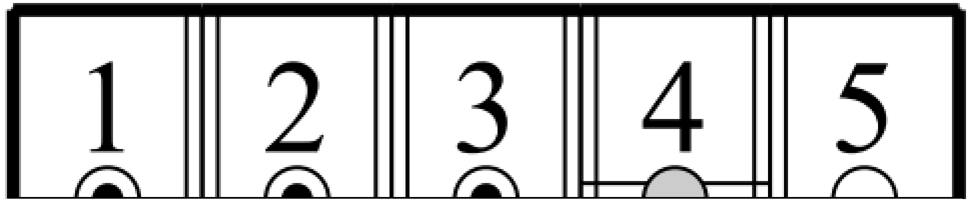


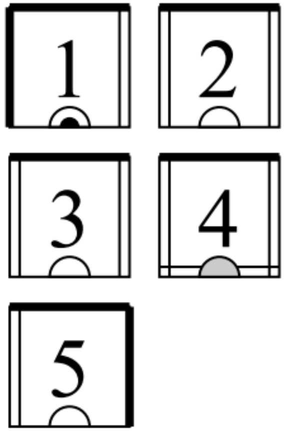
Tile complexity = $2n$

strength-1 glues (with no other glues to cooperate with)

Tile complexity at temperature $\tau = 2$

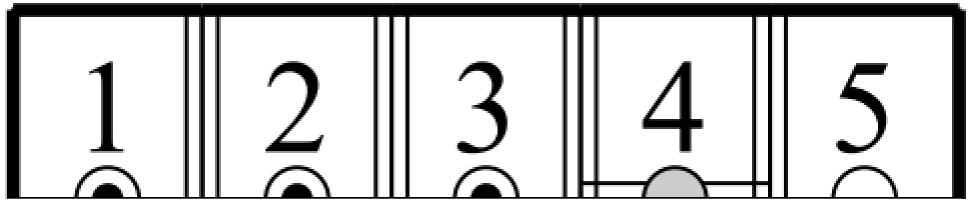
Goal: complete a 1 x *n* line into an *n* x *n* square

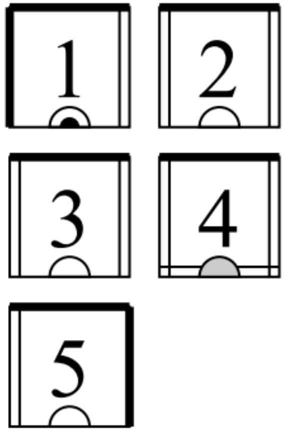


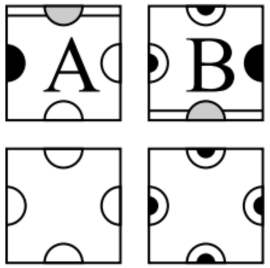


Tile complexity at temperature $\tau = 2$

Goal: complete a 1 x n line into an n x n square

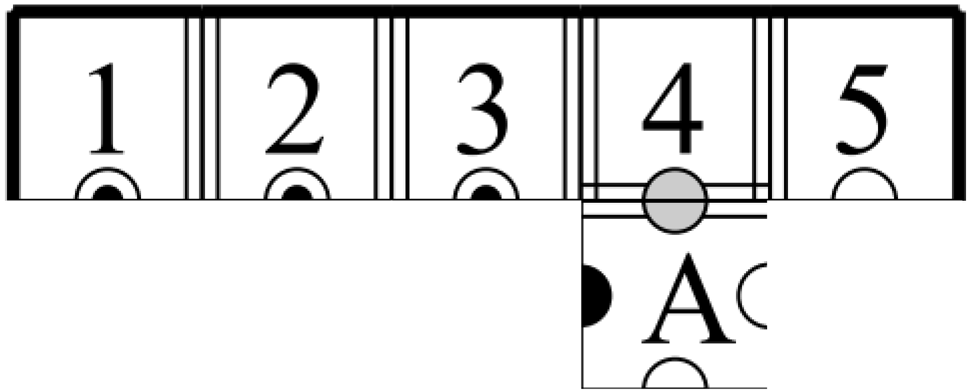


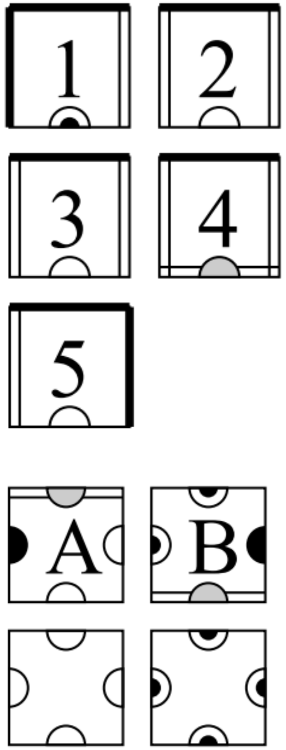




Tile complexity at temperature $\tau = 2$

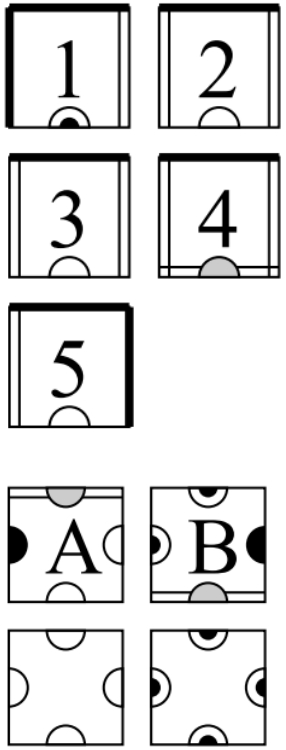
Goal: complete a 1 x *n* line into an *n* x *n* square

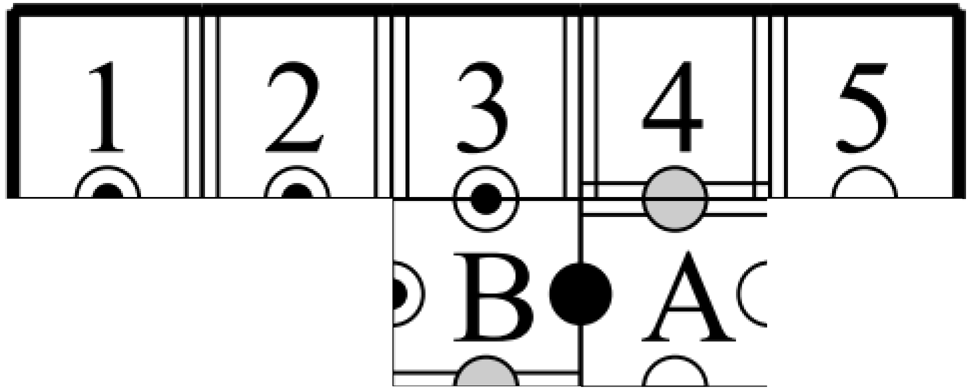




Tile complexity at temperature $\tau = 2$

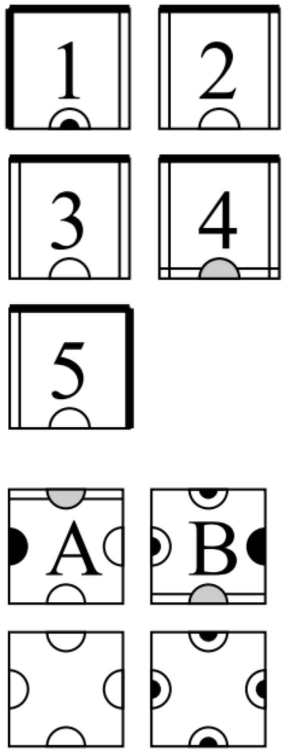
Goal: complete a 1 x n <u>line</u> into an n x n square

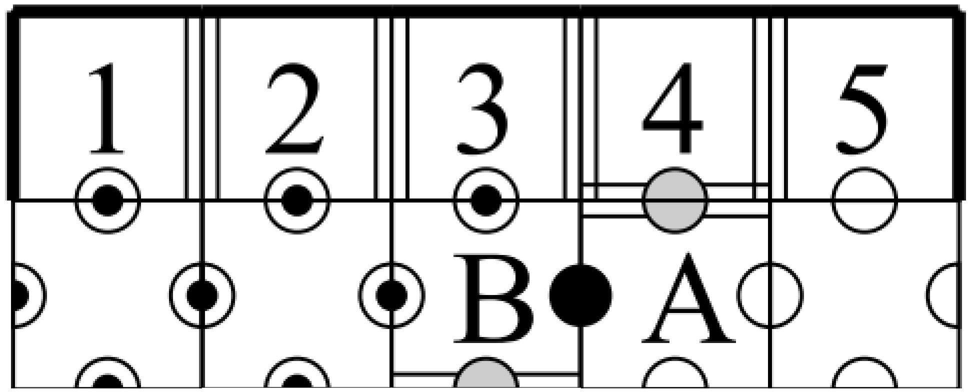




Tile complexity at temperature $\tau = 2$

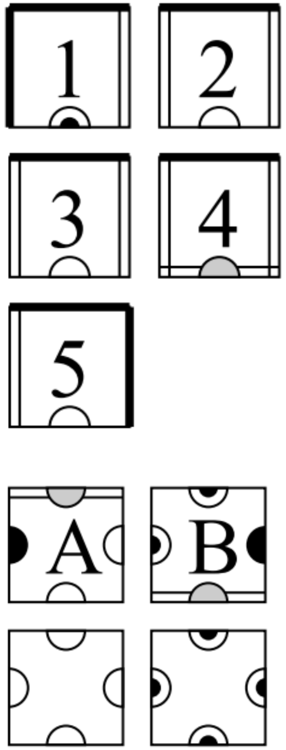
Goal: complete a 1 x *n* line into an *n* x *n* square

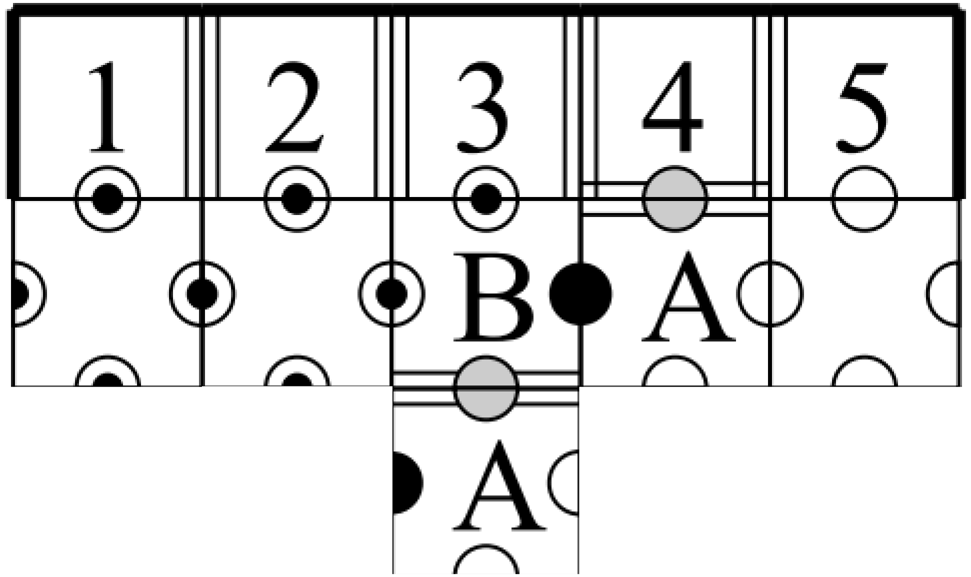




Tile complexity at temperature $\tau = 2$

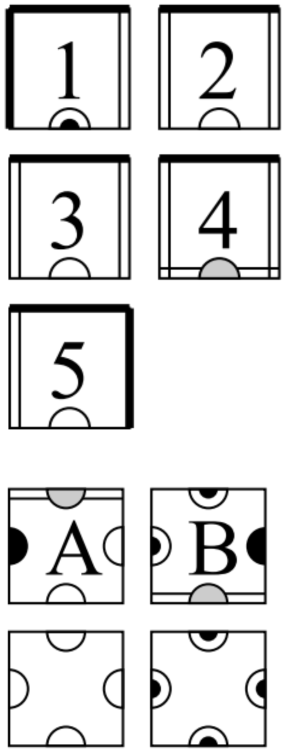
Goal: complete a 1 x *n* line into an *n* x *n* square

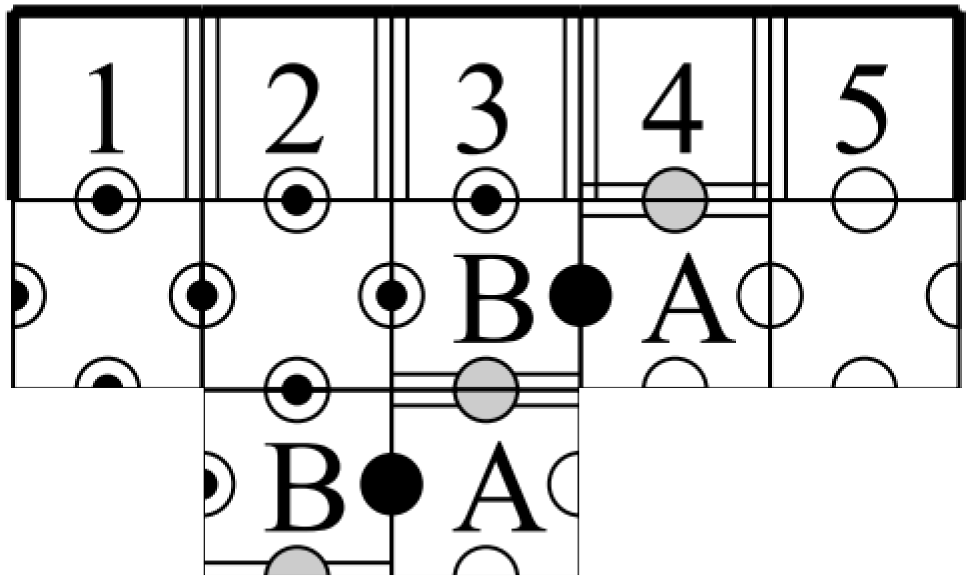




Tile complexity at temperature $\tau = 2$

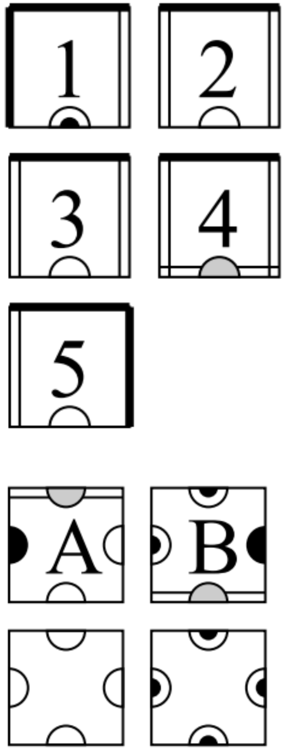
Goal: complete a 1 x *n* line into an *n* x *n* square

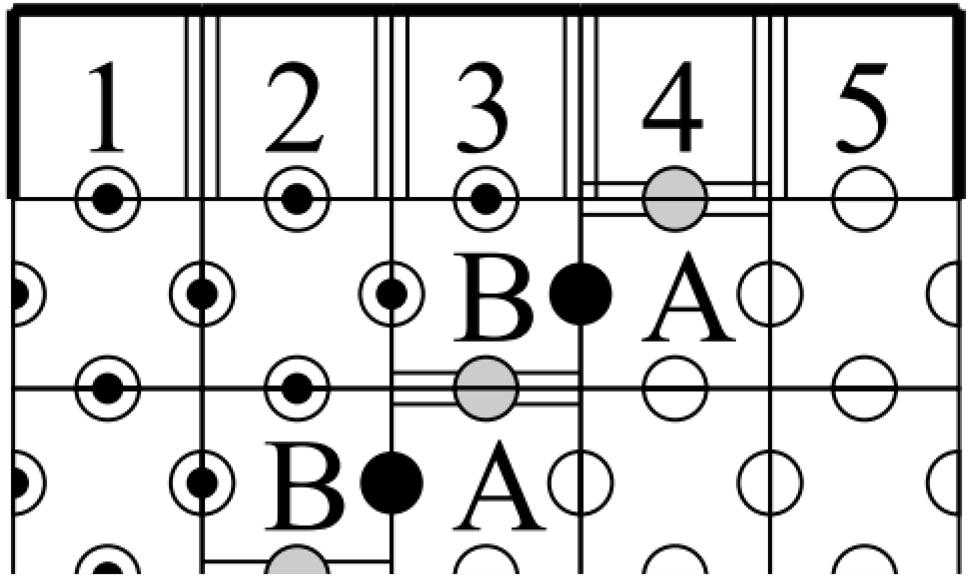




Tile complexity at temperature $\tau = 2$

Goal: complete a 1 x *n* line into an *n* x *n* square





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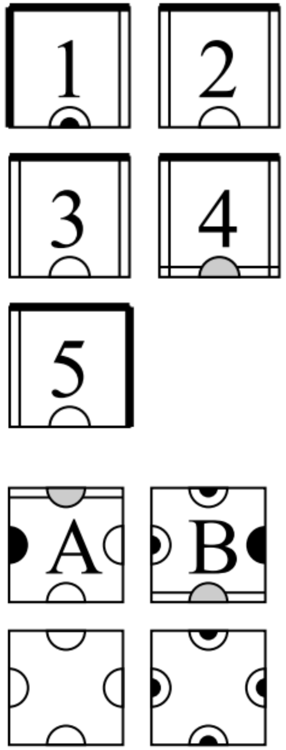
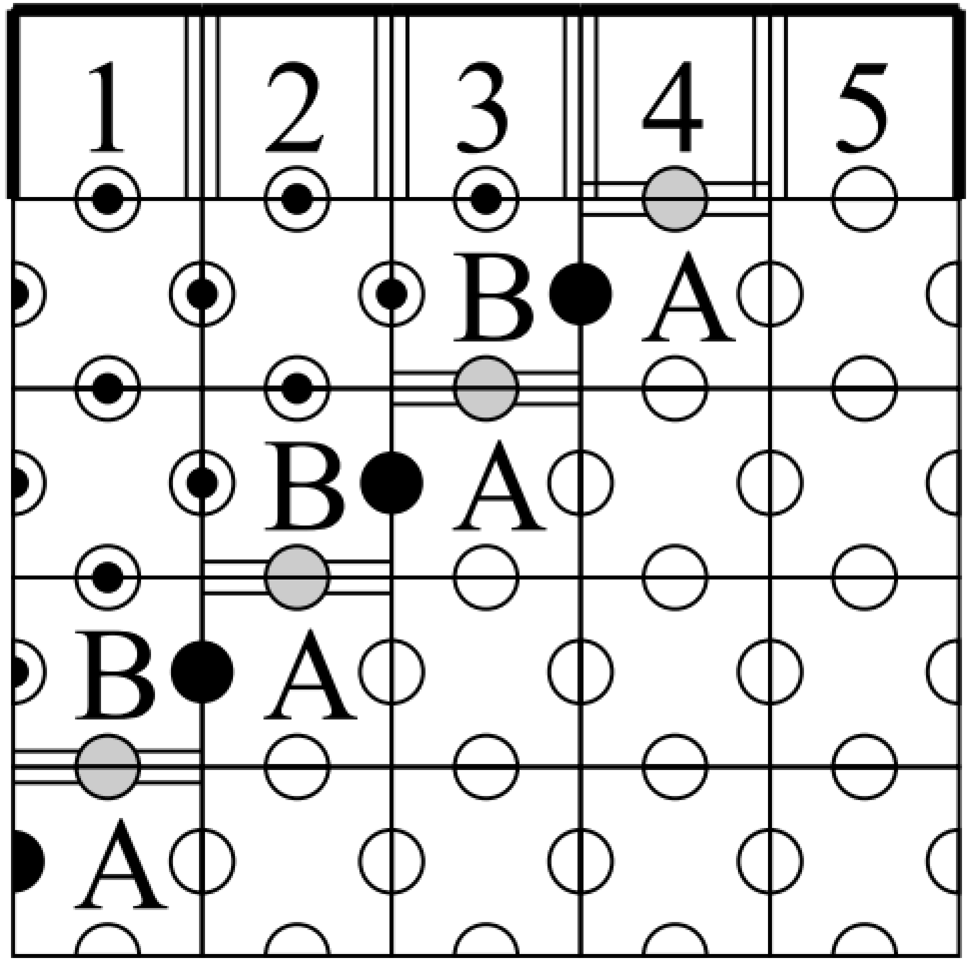
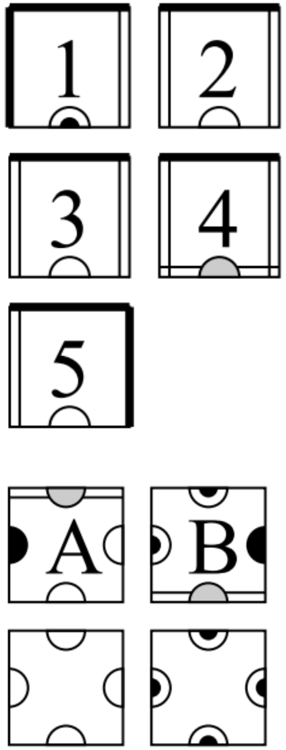
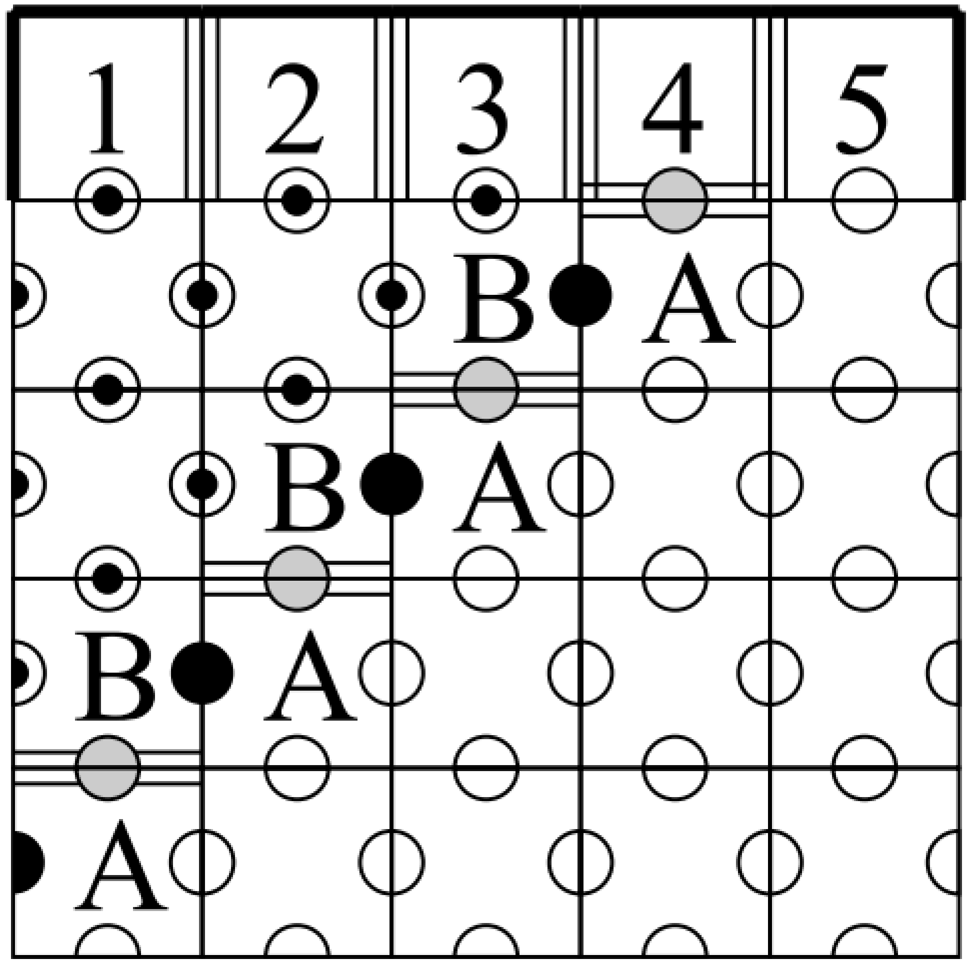




Tile complexity at temperature $\tau = 2$

Goal: complete a 1 x n line into an n x n square

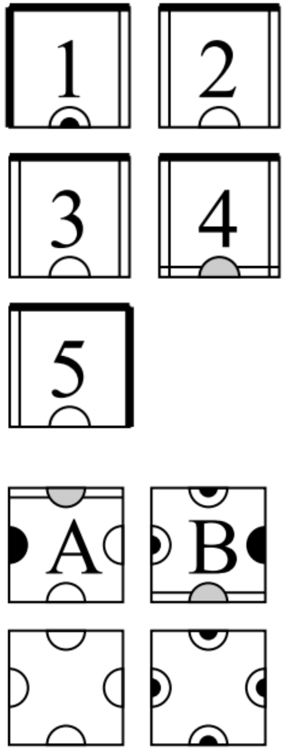


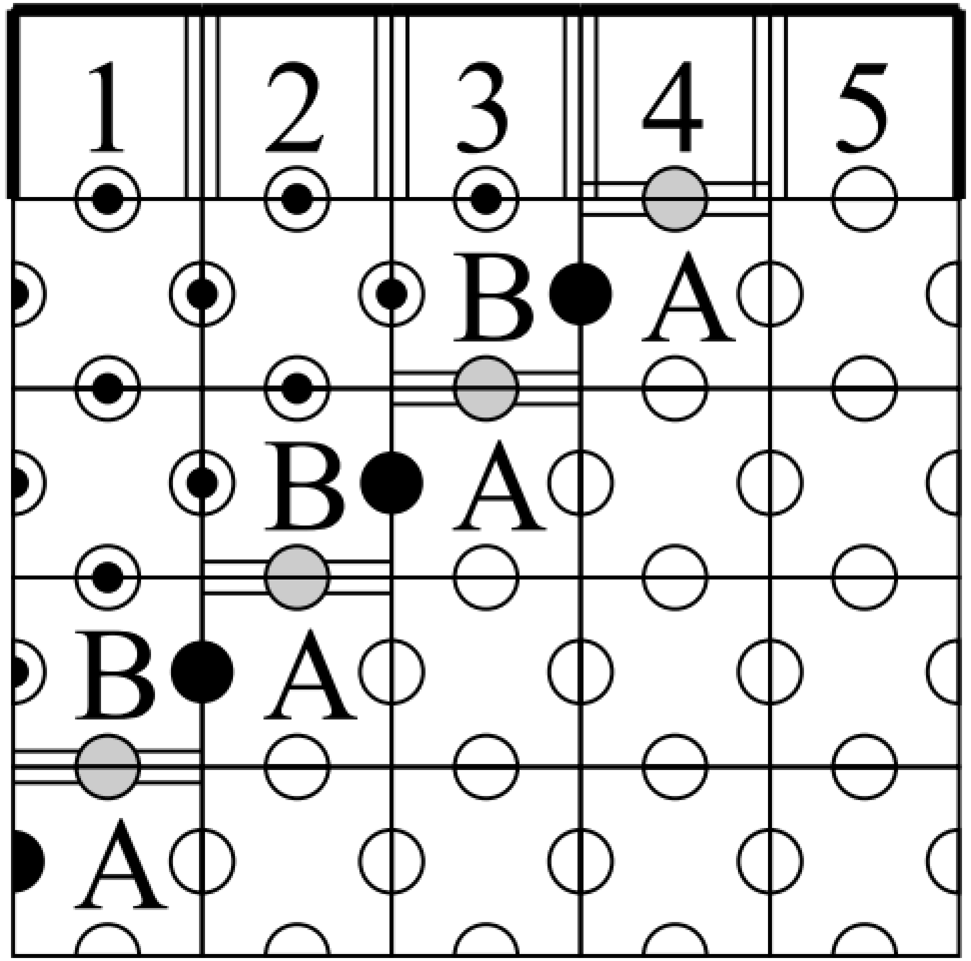


Tile complexity = $n + 4$

Tile complexity at temperature $\tau = 2$

Goal: complete a 1 x n line into an n x n square





Tile complexity = n + 4

How to get *sublinear* tile complexity?

Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types

Logarithmic tile complexity at temperature $\tau = 2$

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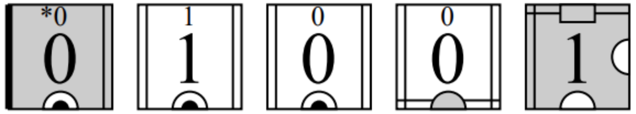
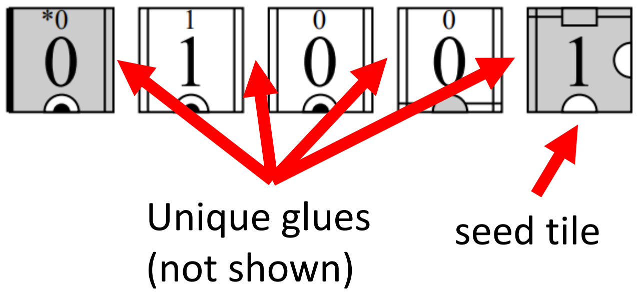


seed tile

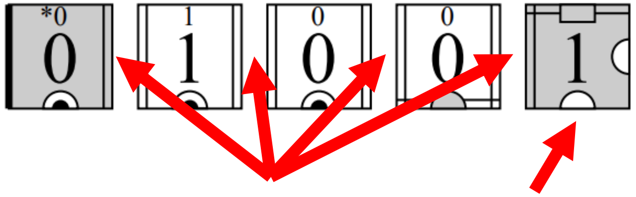
Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types



Logarithmic tile complexity at temperature $\tau = 2$

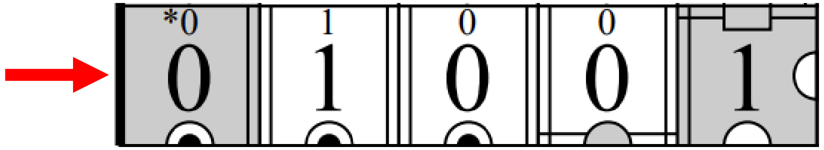
Goal: rectangle of height n using $O(\log n)$ tile types



Unique glues (not shown)

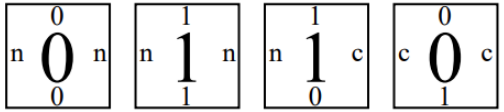
seed tile

row encoding (a number related to) n

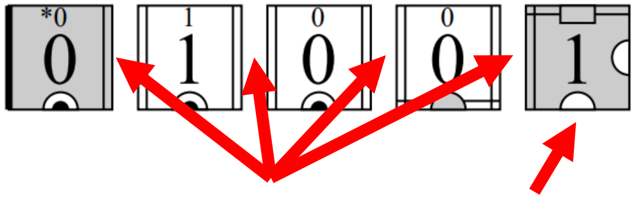


Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height *n* using *O*(log *n*) tile types



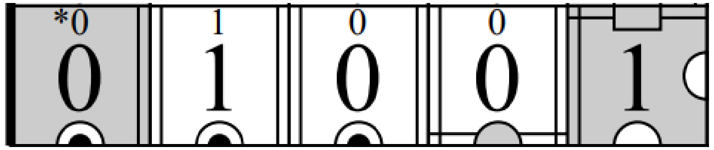
increment tiles



Unique glues (not shown)

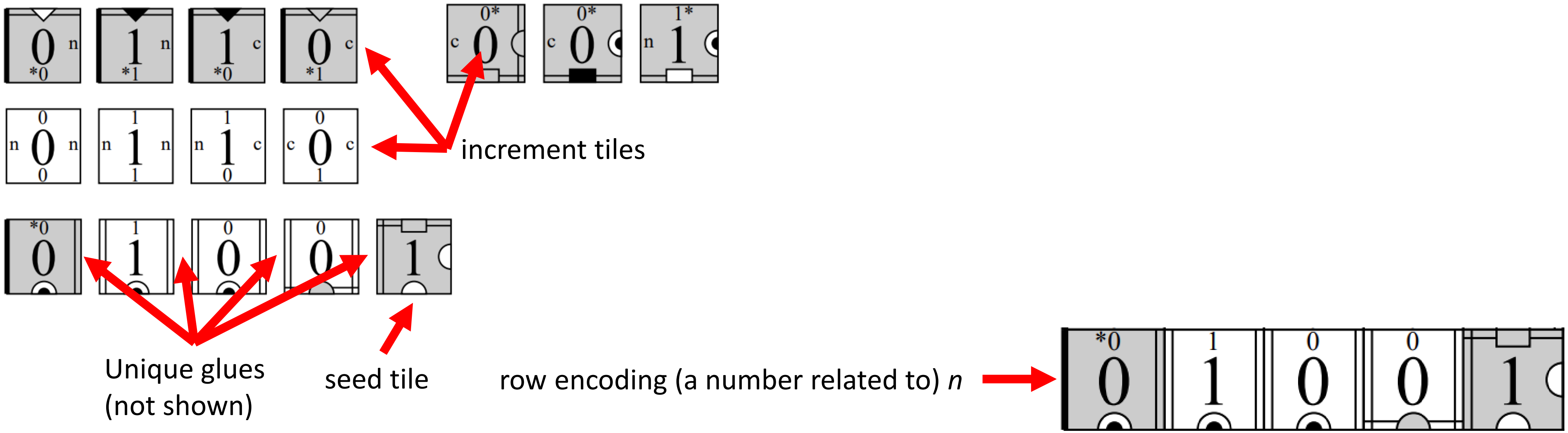
seed tile

row encoding (a number related to) *n*



Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types



Logarithmic tile complexity at temperature $\tau = 2$

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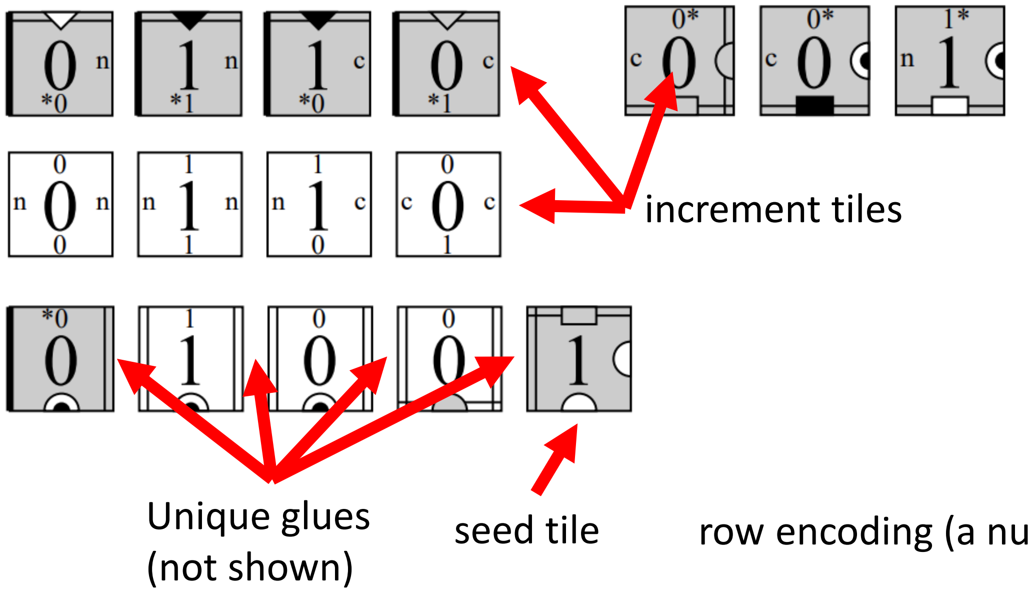
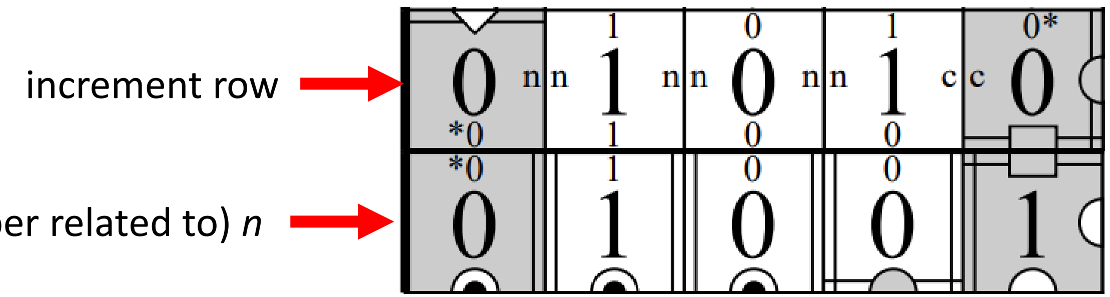
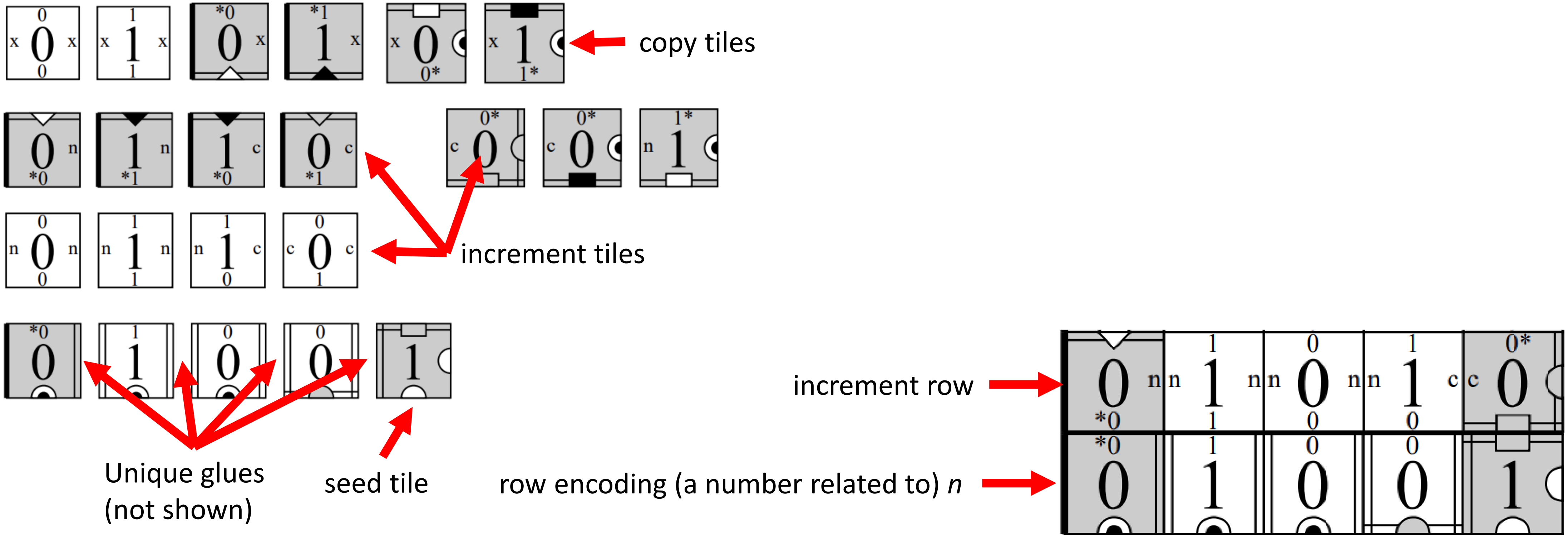




Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types



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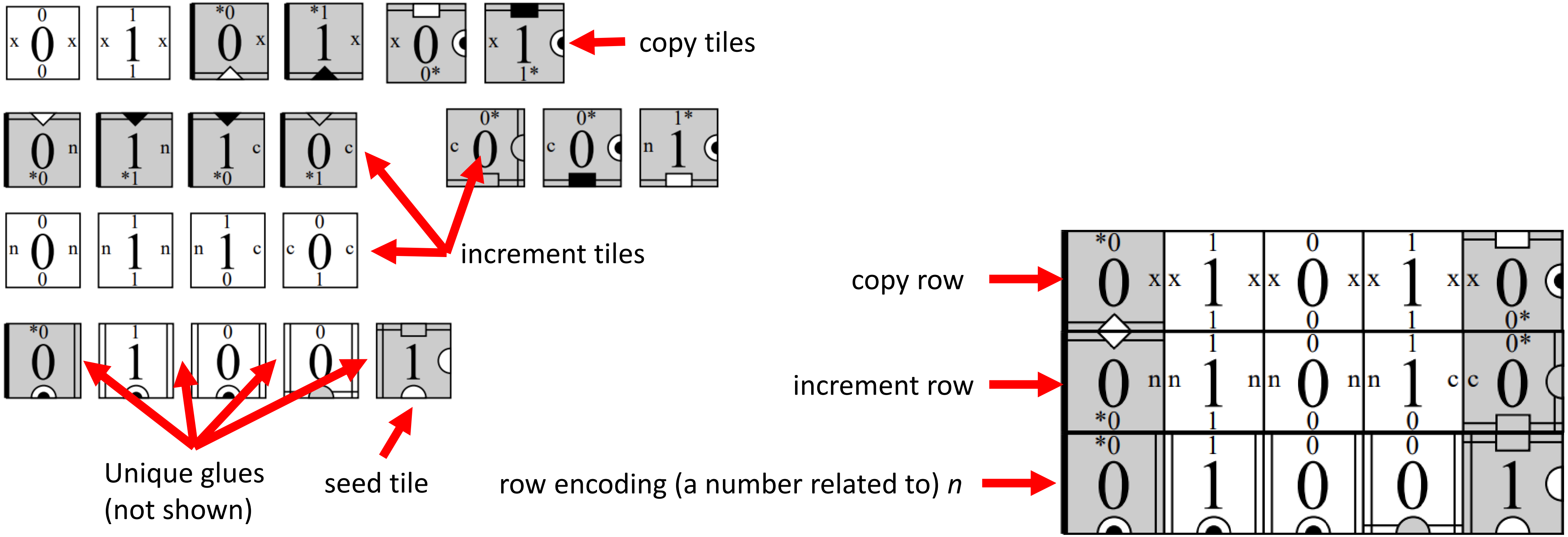

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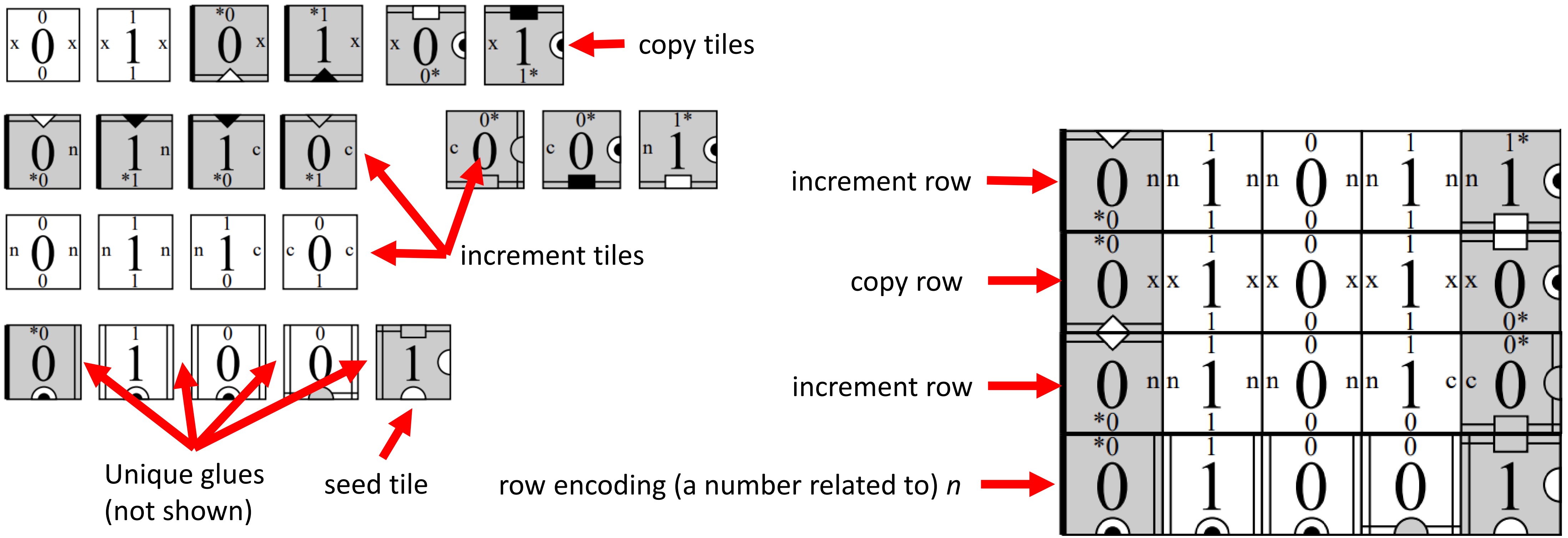

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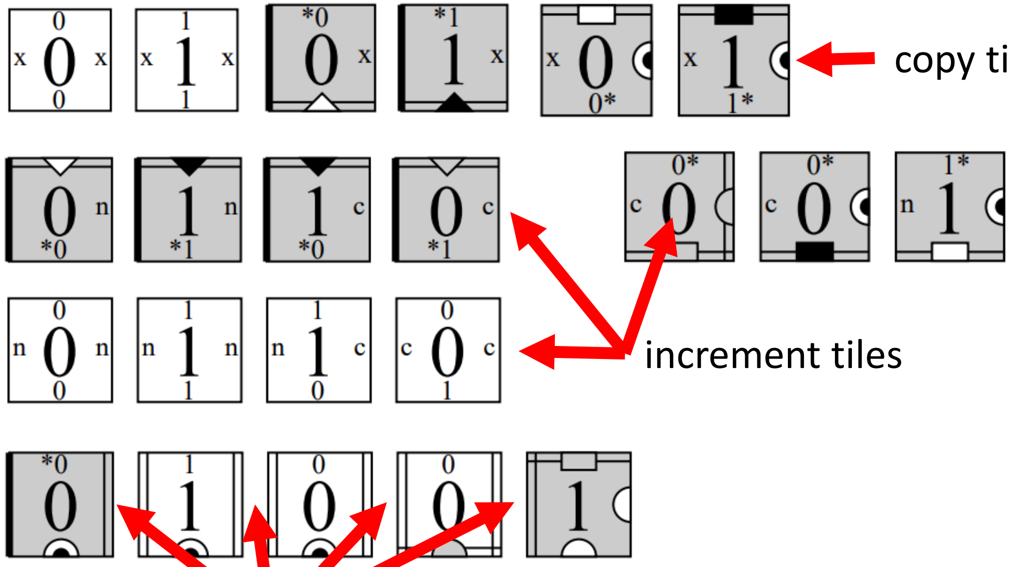
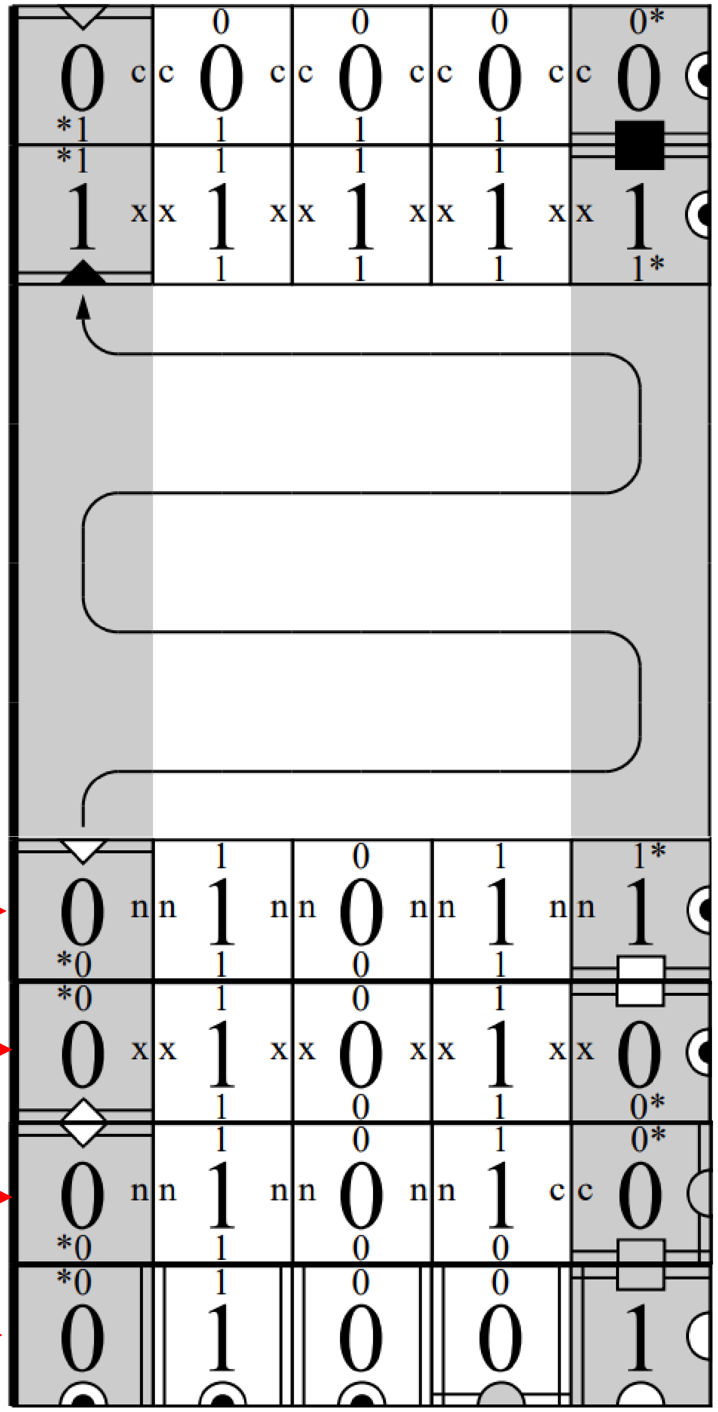


copy tiles

increment tiles

Unique glues (not shown)

seed tile



increment row

copy row

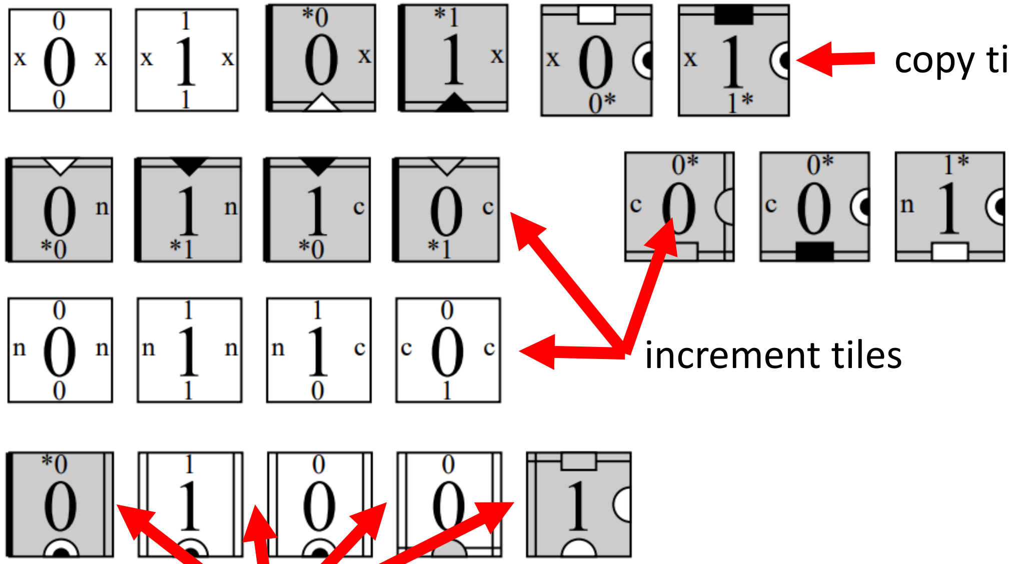
increment row

row encoding (a number related to) *n*

Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types

for width of k bits, stops when it reaches what value?

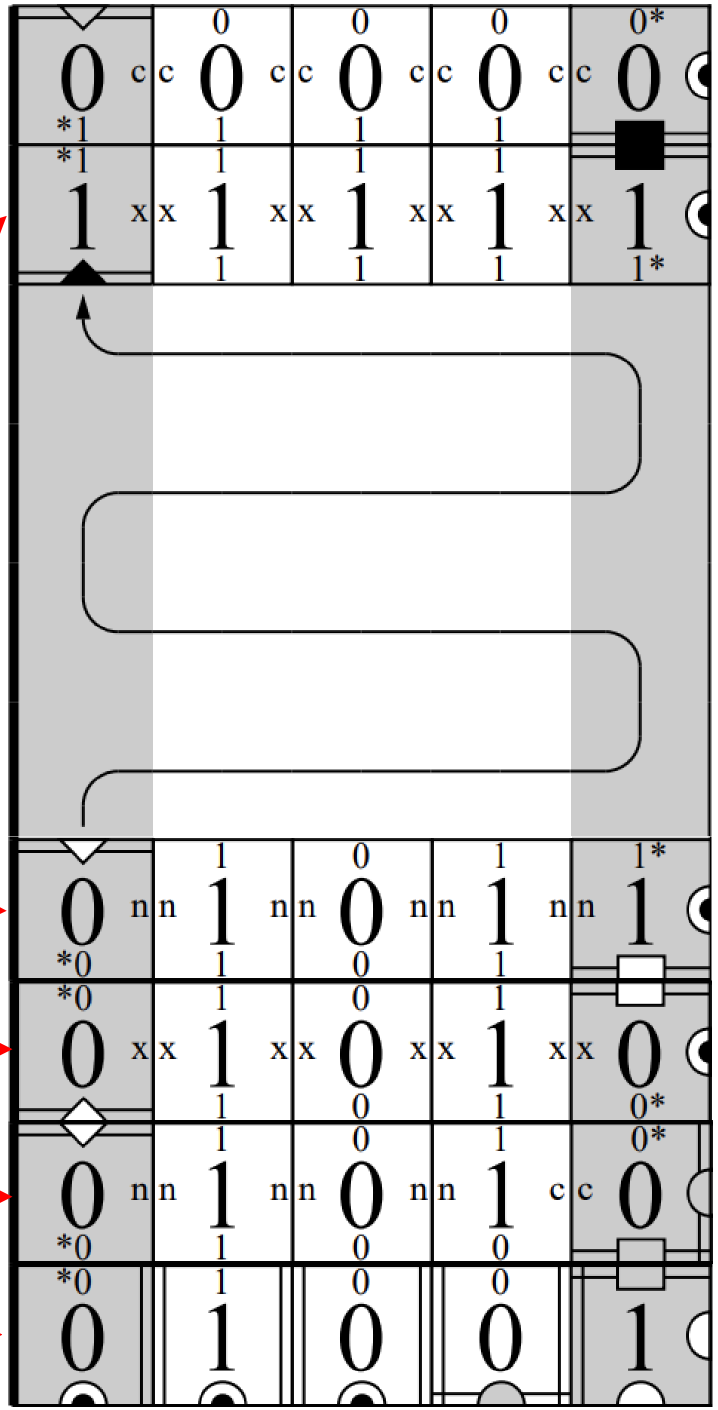


copy tiles

increment tiles

Unique glues (not shown)

seed tile



increment row

copy row

increment row

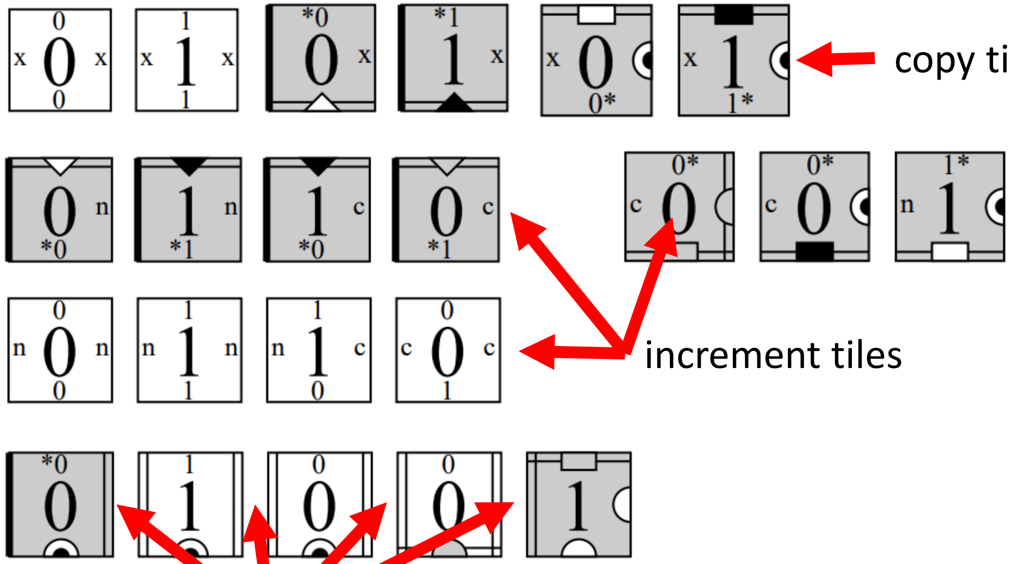
row encoding (a number related to) n

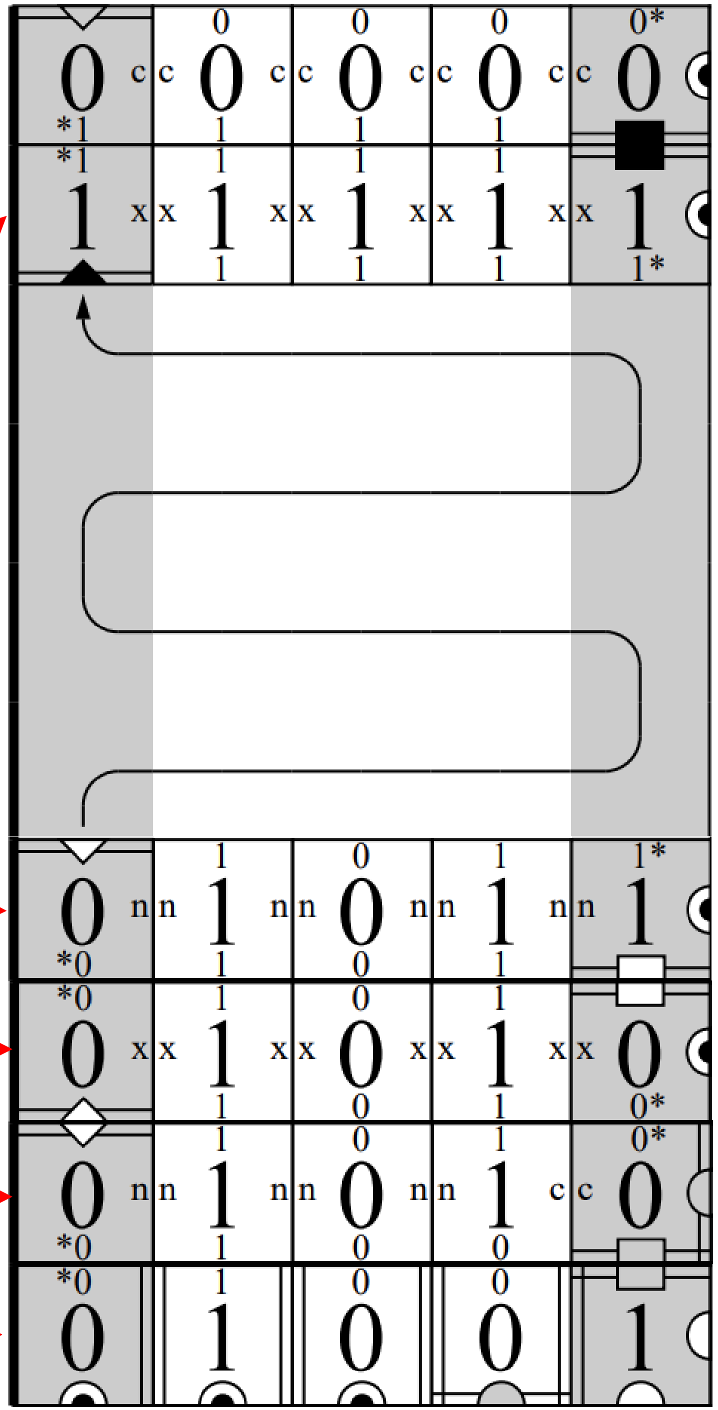
Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types

for width of k bits, stops when it reaches what value?

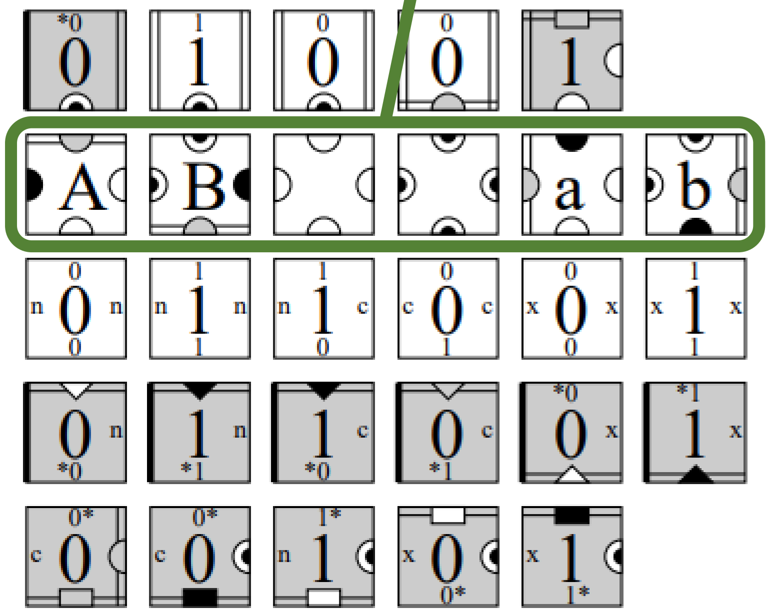
"zig-zag counter"

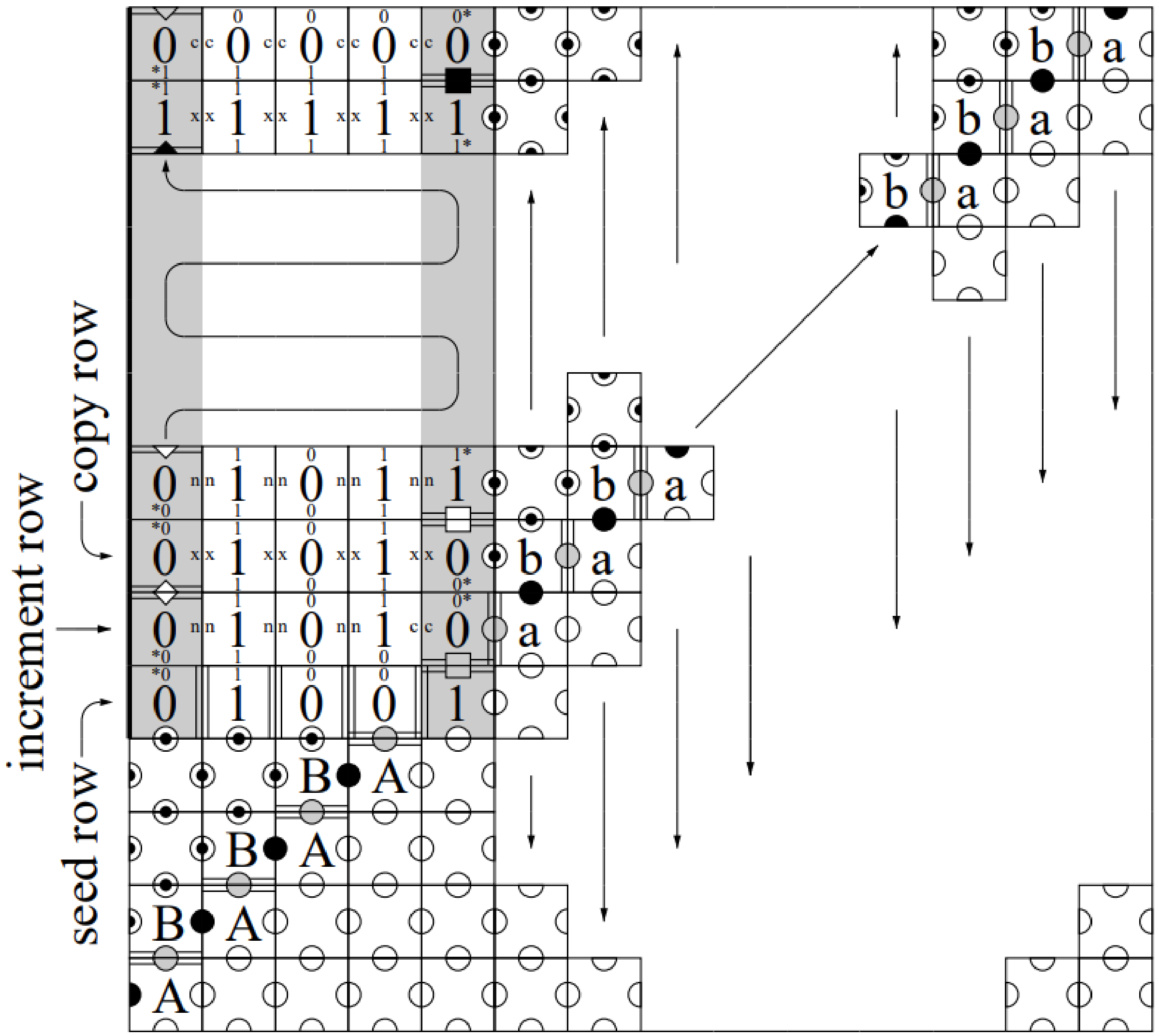




Logarithmic tile complexity at temperature $\tau = 2$

A few more "filler" tiles complete the ≈*n* x log *n* rectangle into an *n* x *n* square.

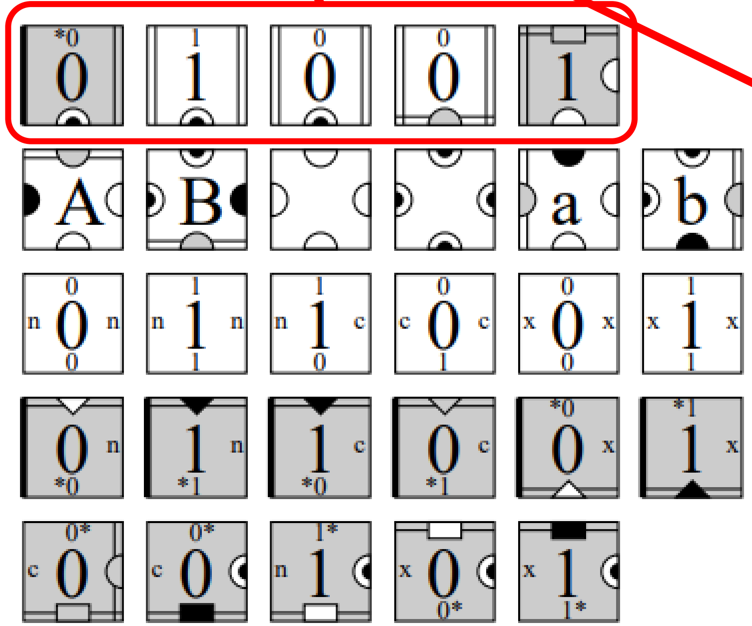


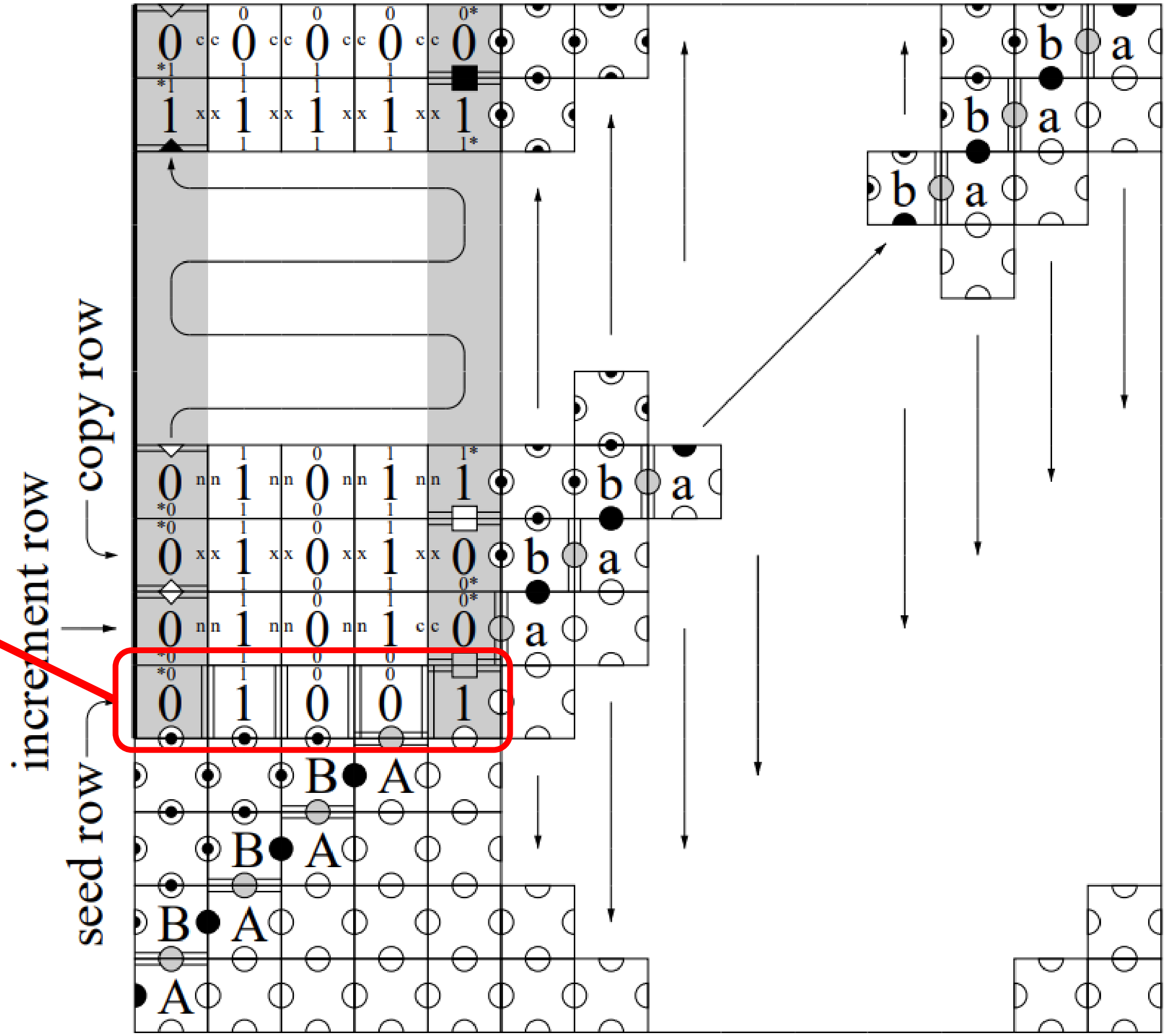


Logarithmic tile complexity at temperature $\tau = 2$

A few more "filler" tiles complete the ≈*n* x log *n* rectangle into an *n* x *n* square.

tile complexity = log *n* + 23

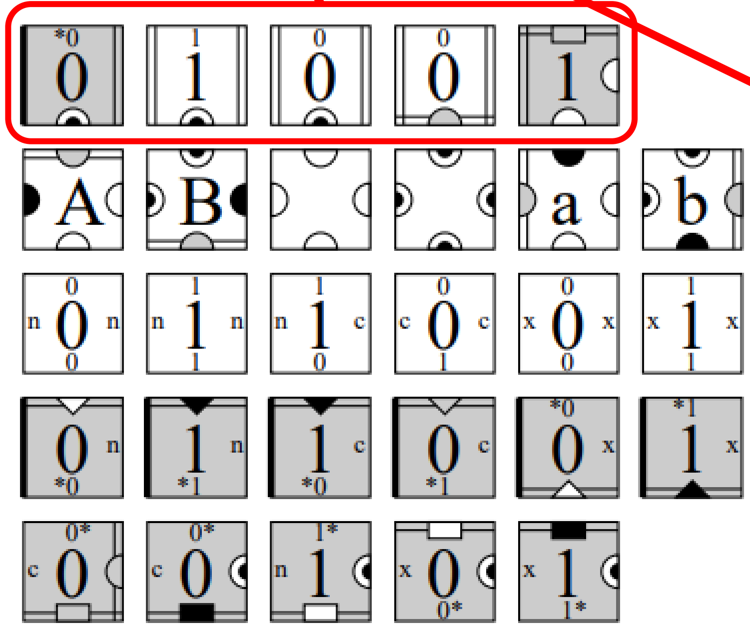


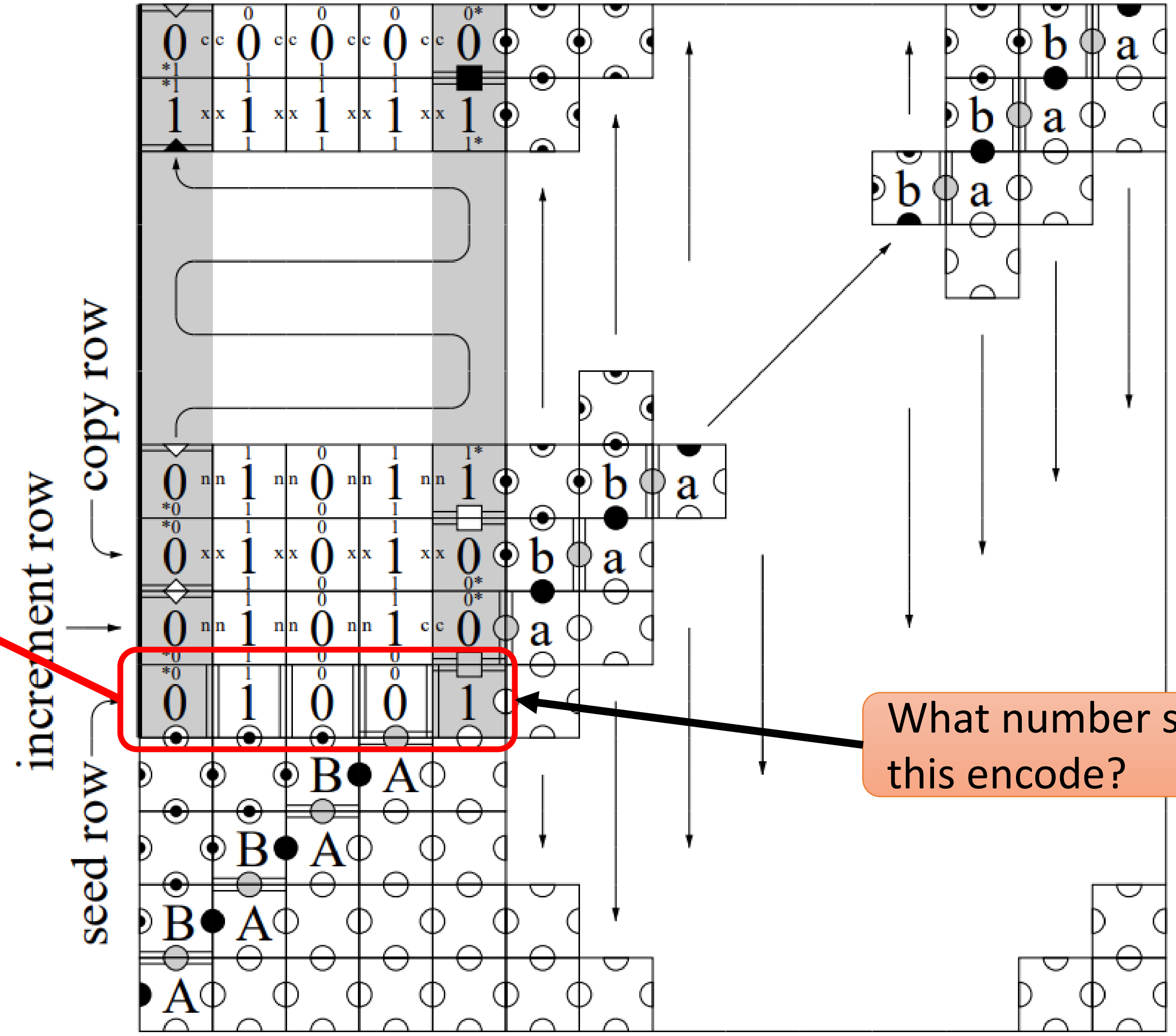


Logarithmic tile complexity at temperature $\tau = 2$

A few more "filler" tiles complete the ≈n x log n rectangle into an n x n square.

tile complexity = log n + 23





What number should this encode?

$\Omega(\log n / \log \log n)$ tile complexity lower bound for n x n squares

$\Omega(\log n / \log \log n)$ tile complexity lower bound for n x n squares

- What does $\Omega(\log n / \log \log n)$ tile complexity lower bound mean?

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  - First let's think about what we already showed: what does $O(\log n)$ tile complexity upper bound mean? **For all *n***, $O(\log n)$ tile types is enough to self-assemble an n x n square.

$\Omega(\log n / \log \log n)$ tile complexity lower bound for n x n squares

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  - A lower bound looks like: **For infinitely many *n***, $o(\log n / \log \log n)$ tile types is not enough to self-assemble an n x n square.

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- How to prove? It's a counting argument:

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    - We'll show that it's fewer than p.

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- How to prove? It's a counting argument:
  - Count number of (functionally distinct) tile systems with fewer than ¼ $\log p / \log \log p$ tile types.
    - We'll show that it's fewer than p.
  - There are p squares with width n between $p+1$ and $2p$; each needs a different tile system.

$\Omega(\log n / \log \log n)$ tile complexity lower bound for n x n squares

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  - There are p squares with width n between p+1 and 2p; each needs a different tile system.
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  - Since $p \leq n/2$, we have $\frac{1}{4} \log p / \log \log p \leq \frac{1}{4} \log n / \log \log n$.

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  - Since $p \leq n/2$, we have ¼ $\log p / \log \log p \leq$ ¼ $\log n / \log \log n$.
  - Since we can do this for every positive integer p, there are infinitely many n that require more than ¼ $\log n / \log \log n$ tile types (a stronger result holds: "most" values of n require that many)

How many tile systems with *k* tile types?

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- **Goal**: show that there are fewer than p (“functionally distinct”) tile systems with $k = \frac{1}{4} \log p / \log \log p$ tile types.

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- How many tile systems? $c \cdot d = k(4k)^{4k}$

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- Recall $k = ¼ \log p / \log \log p$; by algebra (see notes), $k^2(4k)^{4k} < p$.

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- By pigeonhole principle, for some width n with $p < n \leq 2p$, the n x n square is not self-assembled by one of these $k^2(4k)^{4k}$ tile systems. Since those are all the tile systems with at most k tile types, the n x n square requires **more** than ¼ log p / log log p tile types to self-assemble. **QED**

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Note: we're ignoring glue strengths here; adds 2 bits per glue to describe at temperature 2.
(since there are 3 possible strengths 0, 1, 2);
see http://doi.org/10.1007/s00453-014-9879-3 for handling higher-temperature systems.

Which bound is tight?

1. All n x n squares can be assembled with $O(\log n)$ tile types; can we get it down to $O(\log n / \log \log n)$?
2. Or do we need $\Omega(\log n)$ tile types to assemble infinitely many n x n squares?

Improved upper bound: self-assembling an n x n square with $O(\log n / \log \log n)$ tile types

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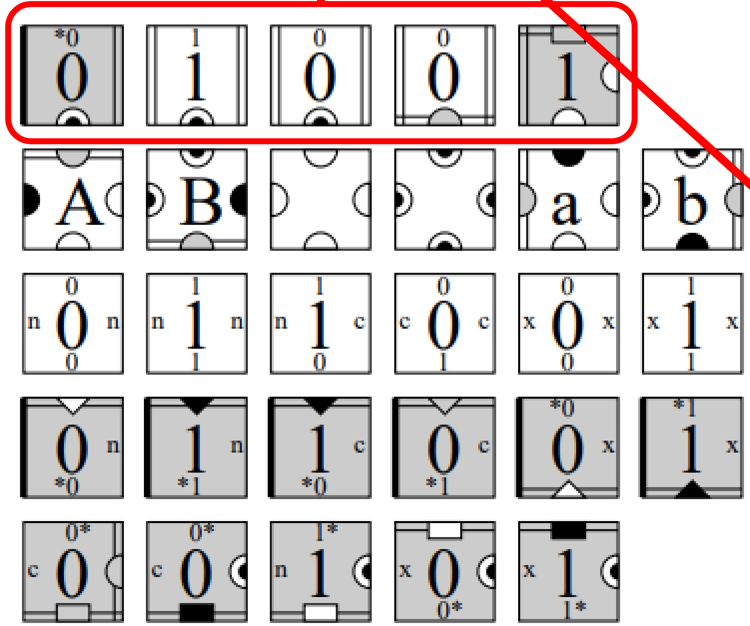
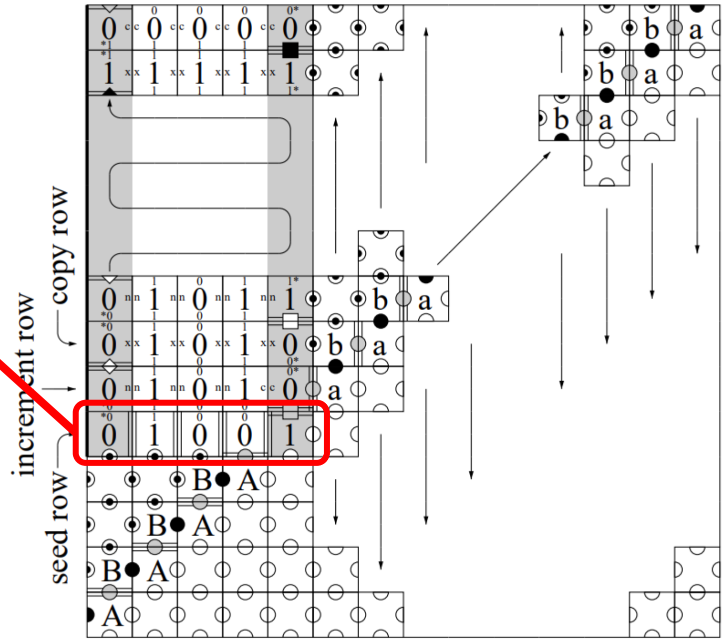
Recall:

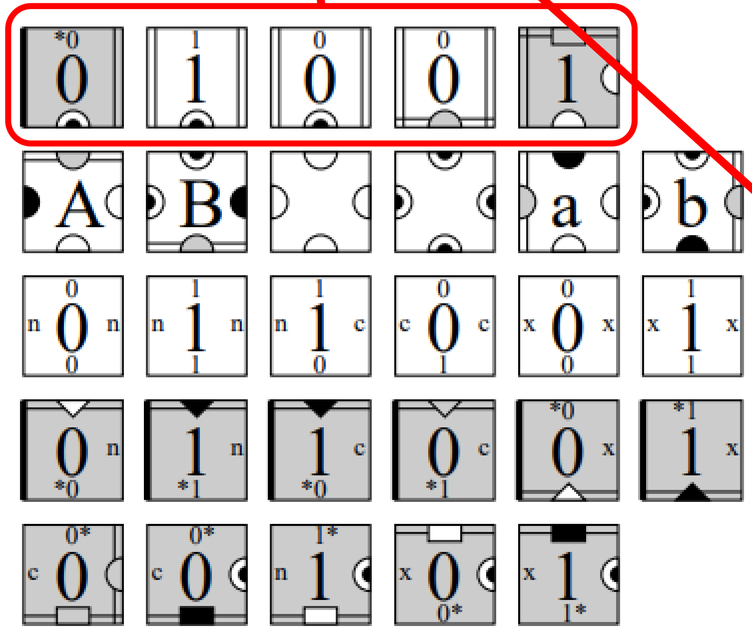
tile complexity = $O(\log n)$ + 23





Improved upper bound: self-assembling an n x n square with $O(\log n / \log \log n)$ tile types

tile complexity = $\boxed{O(\log n)}$ + 23



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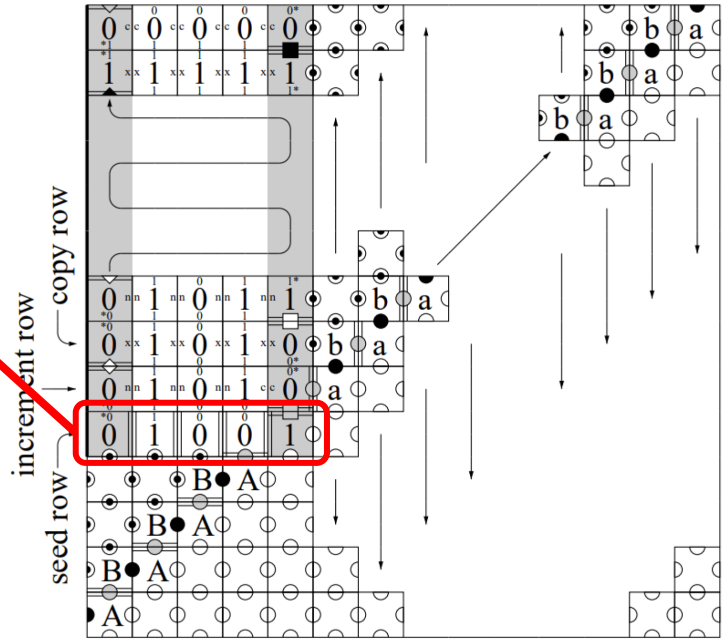

Idea:

1) Use same 23 tiles that turn the seed row encoding a binary integer n' (related to n) into an n x n square.

2) Create the binary seed row from only $\log n / \log \log n$ tiles.

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- Each base-b digit is k bits
  - e.g., if b=2^3=8, then 0=000 1=001 2=010 3=011 4=100 5=101 6=110 7=111
  - e.g., the octal number 7125_8 in binary is 111001010101_2

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  - need $\log(n) / k = \log(n) / \log(\log n / \log \log n) = \log(n) / (\log \log n - \log \log \log n) \approx \log(n) / \log \log n$ base-b digits.

Creating a row of log *n* glues with arbitrary bit string *s* ∈ {0,1}* using log *n* / log log *n* tile types (i.e., base conversion from *b* to 2)

s = 110 001 011 101
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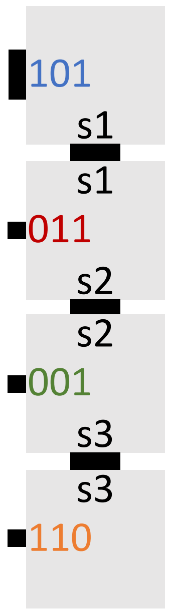
hard-coded tiles:



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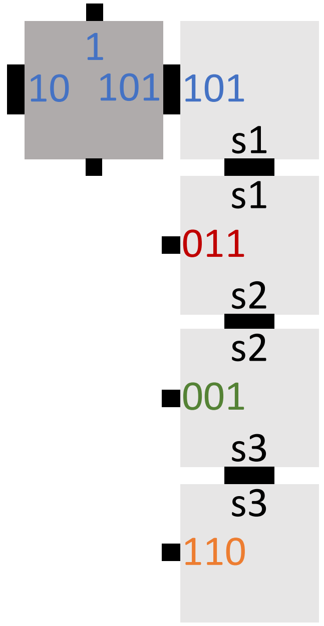

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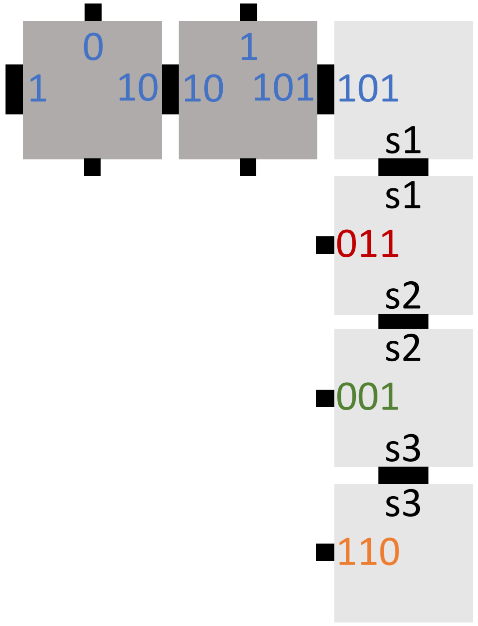

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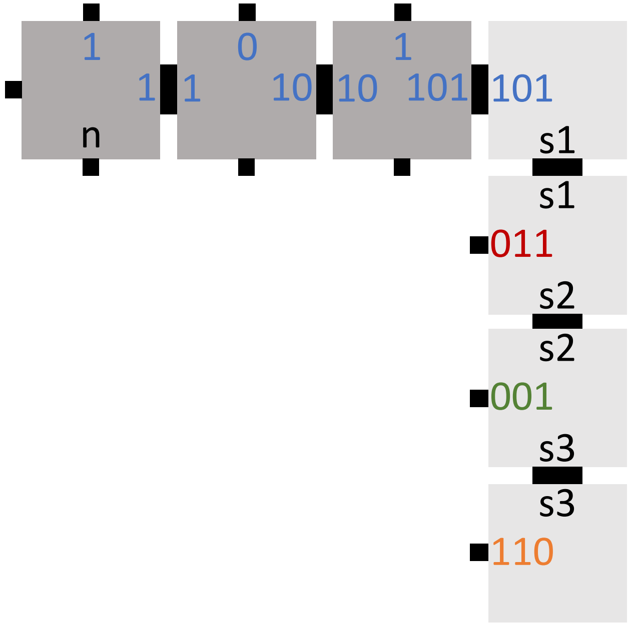

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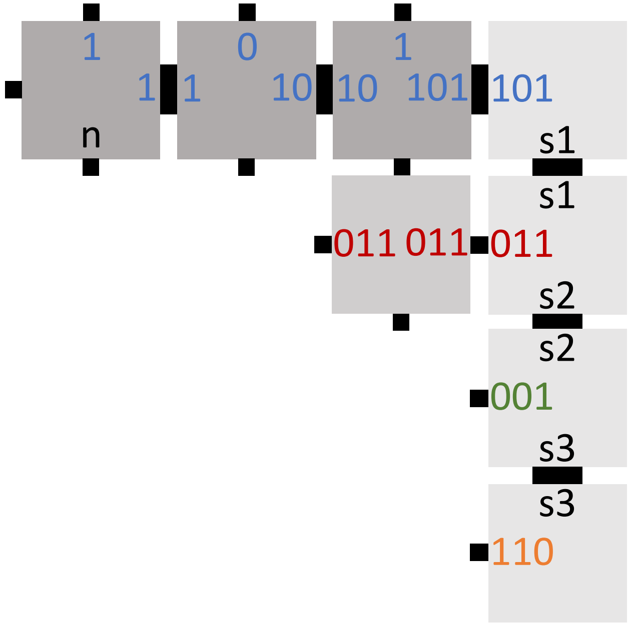

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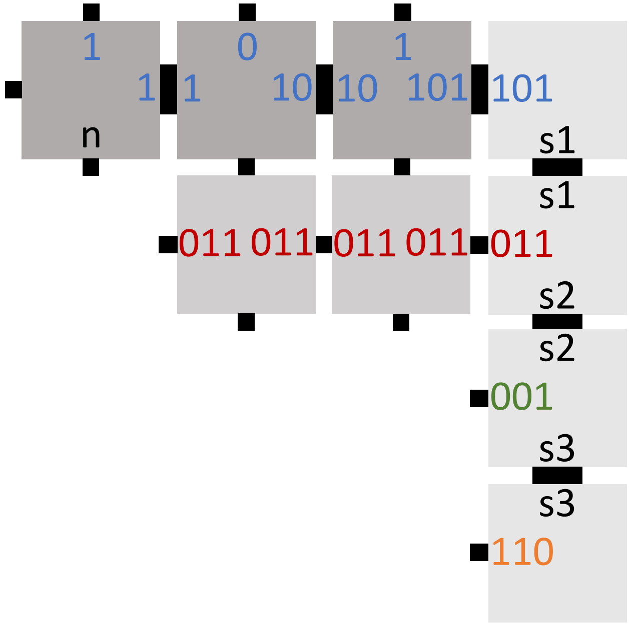

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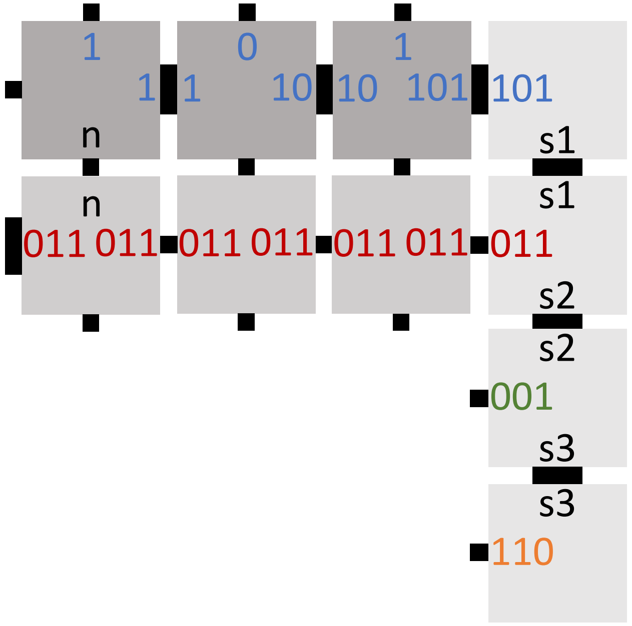

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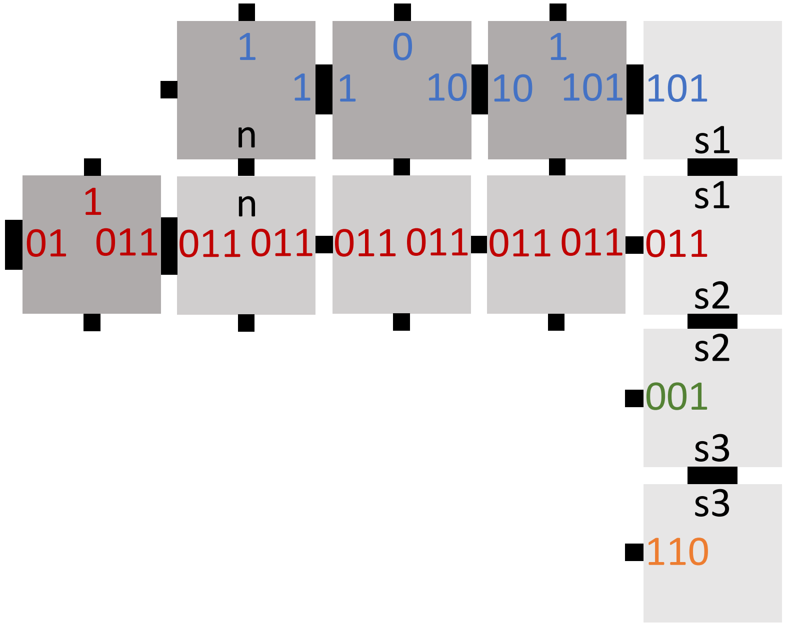

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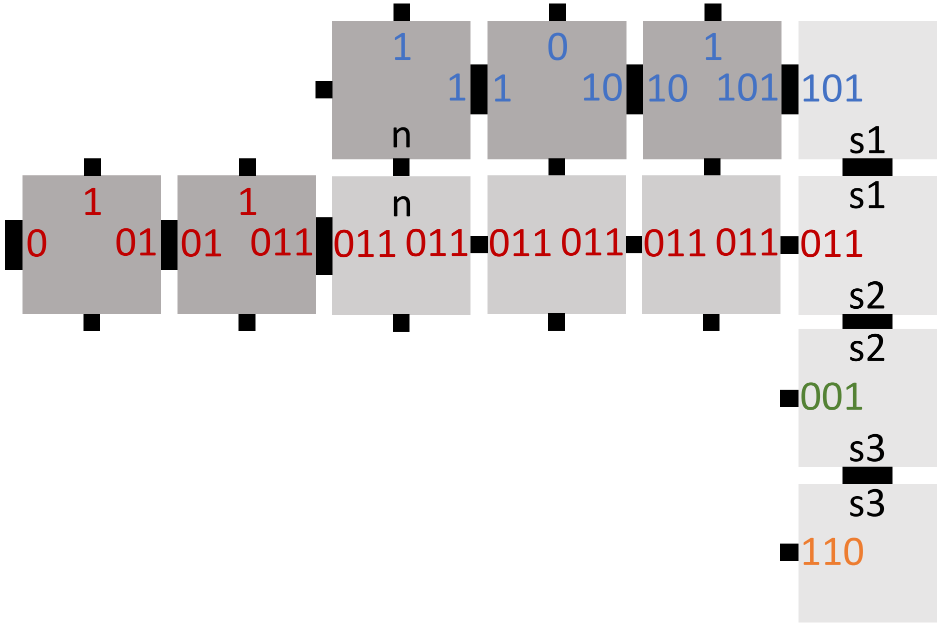

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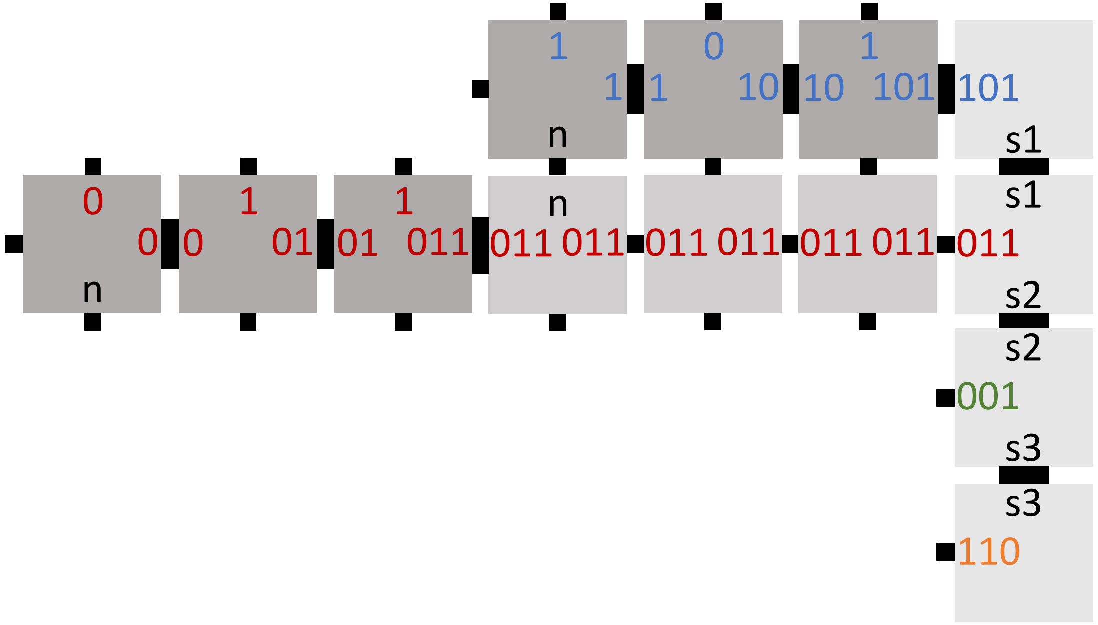

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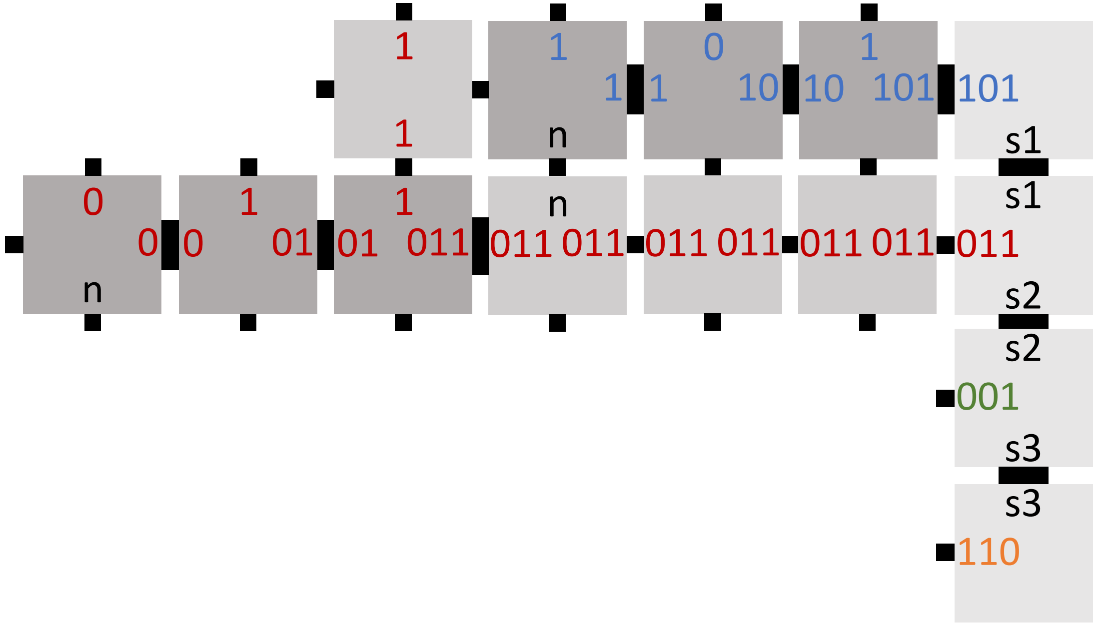

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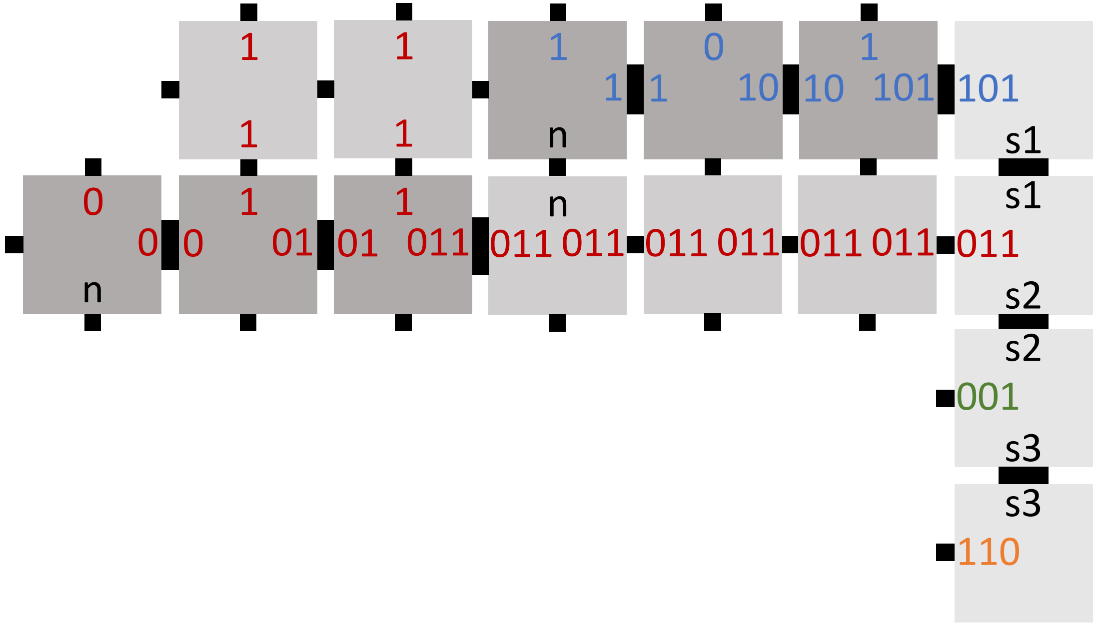

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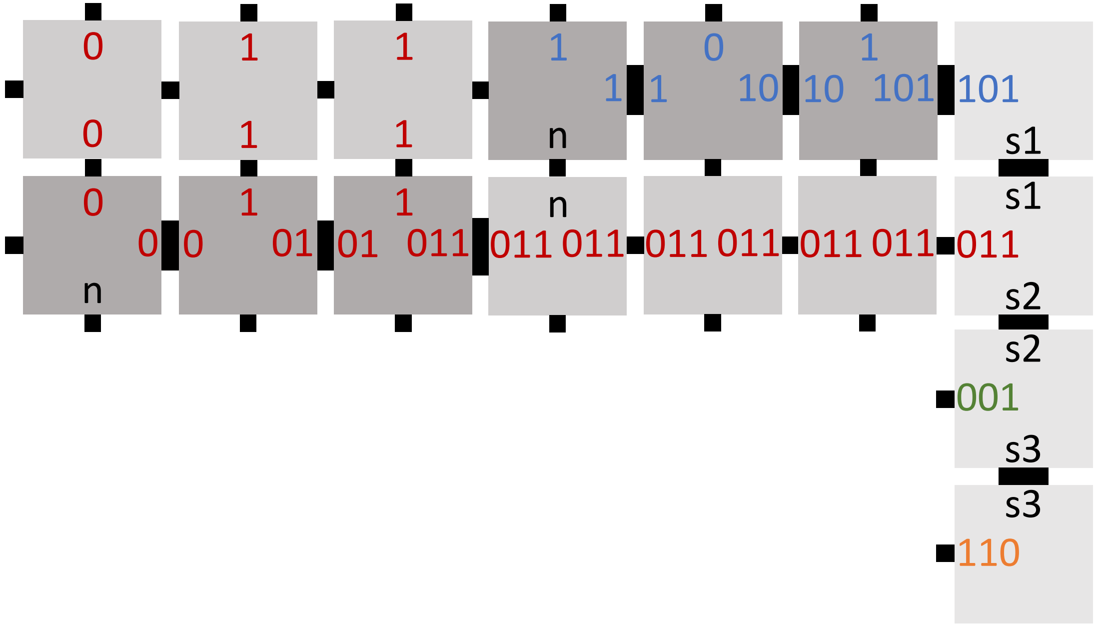

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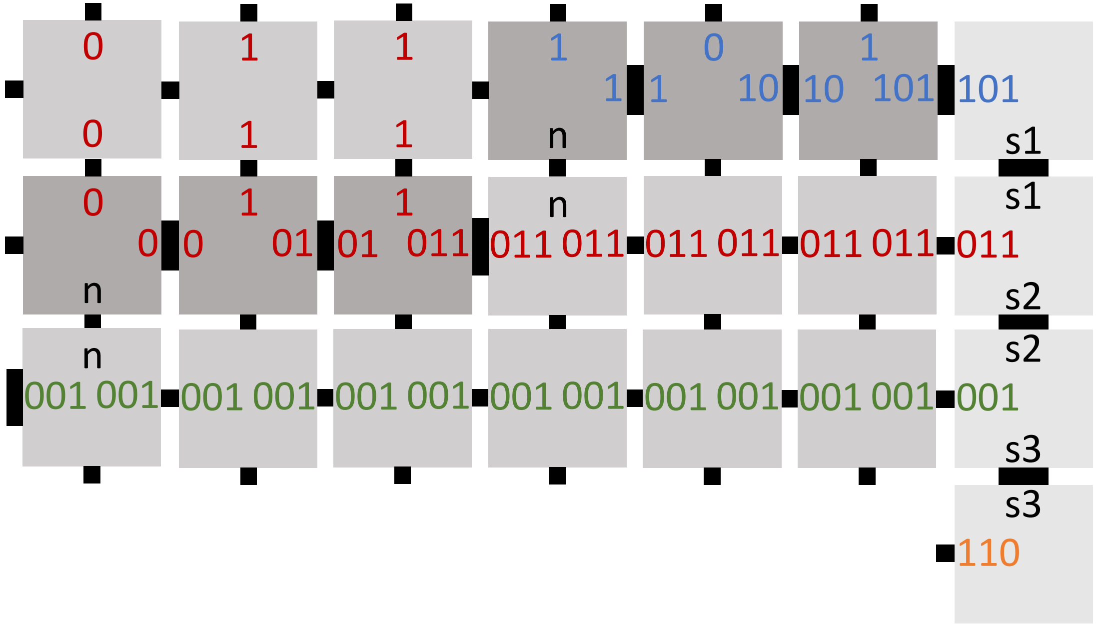

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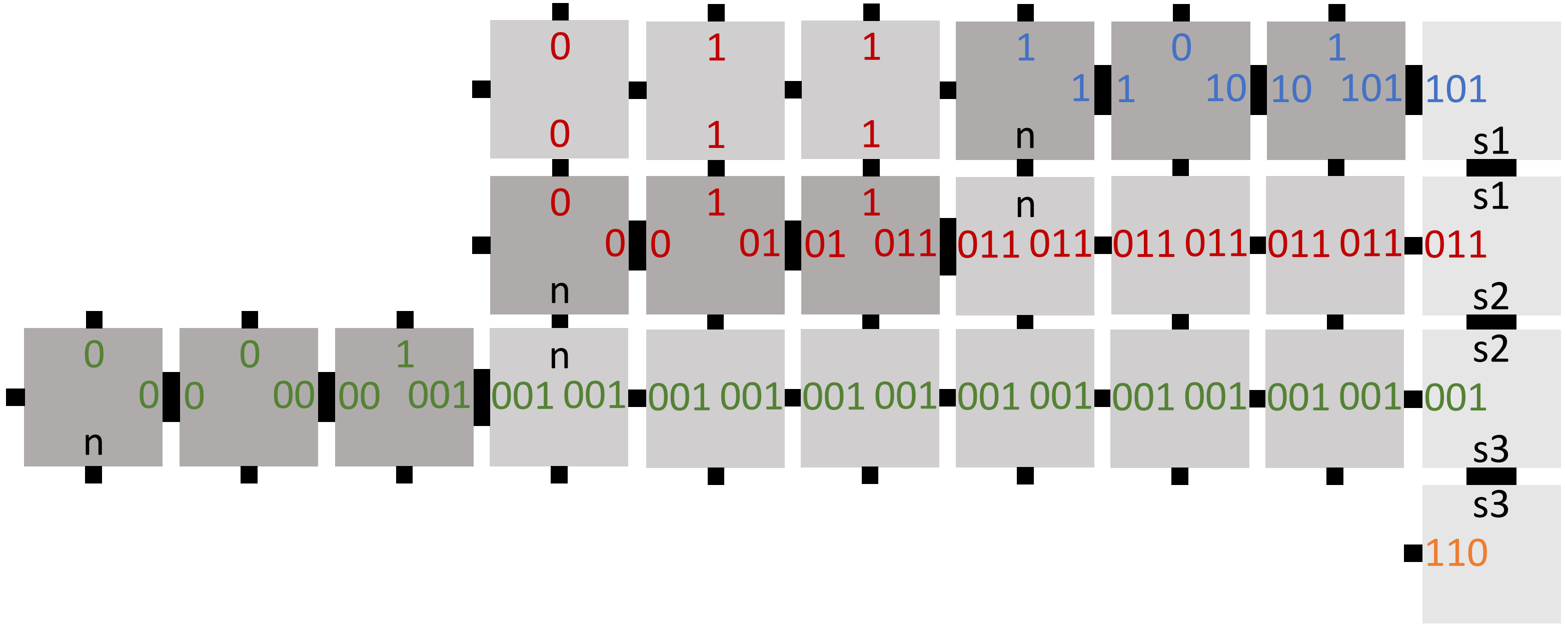

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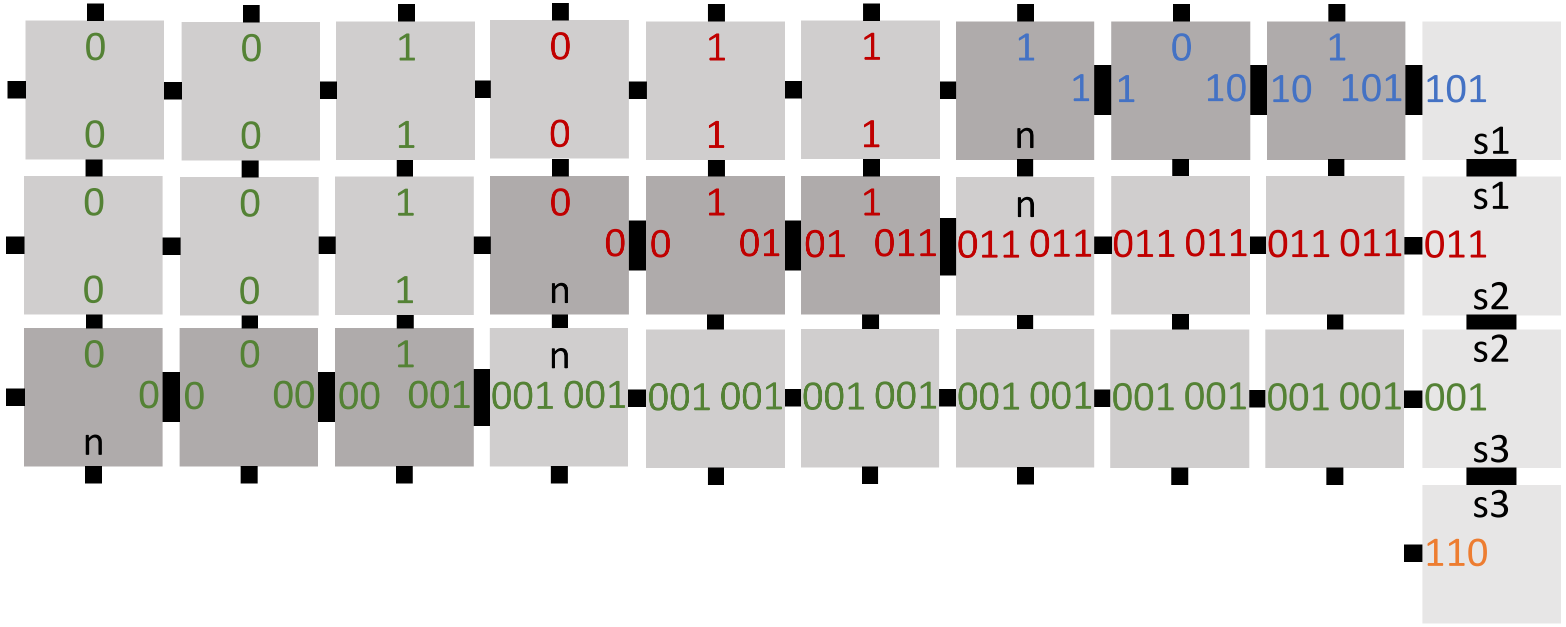

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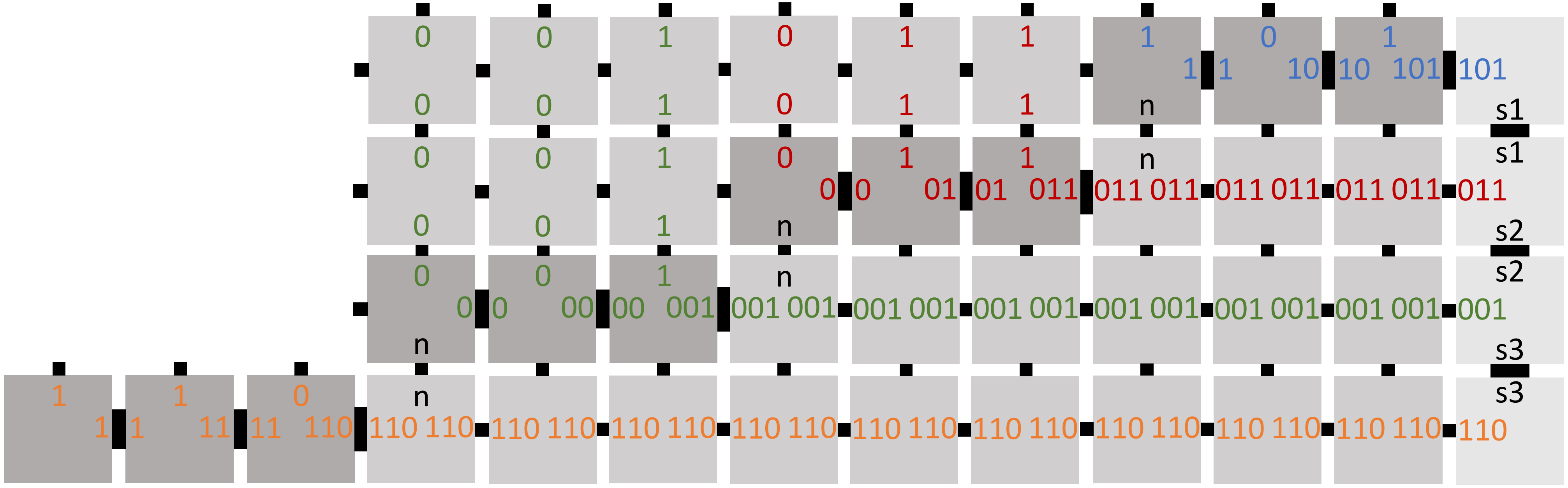

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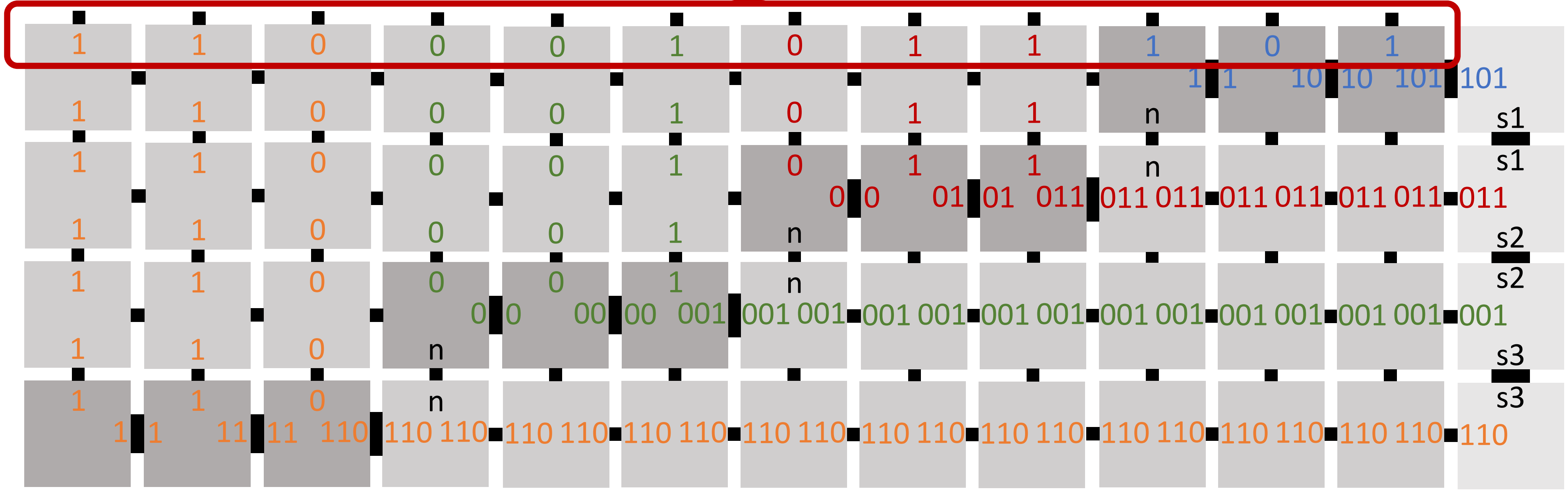

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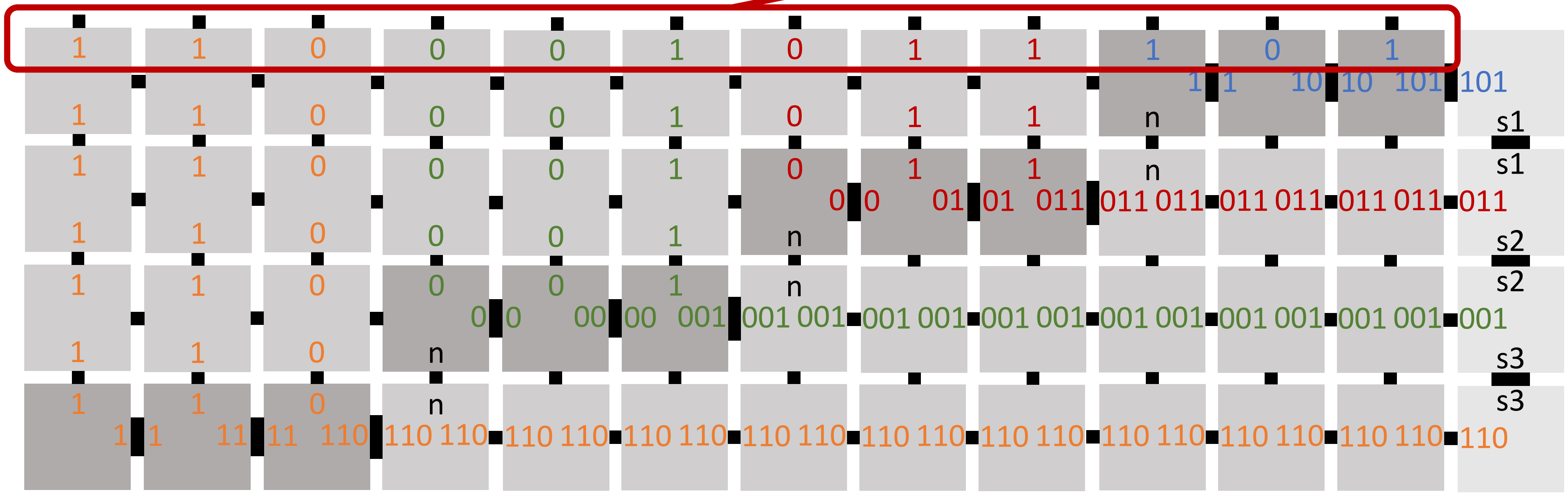

“almost” works… what’s missing?

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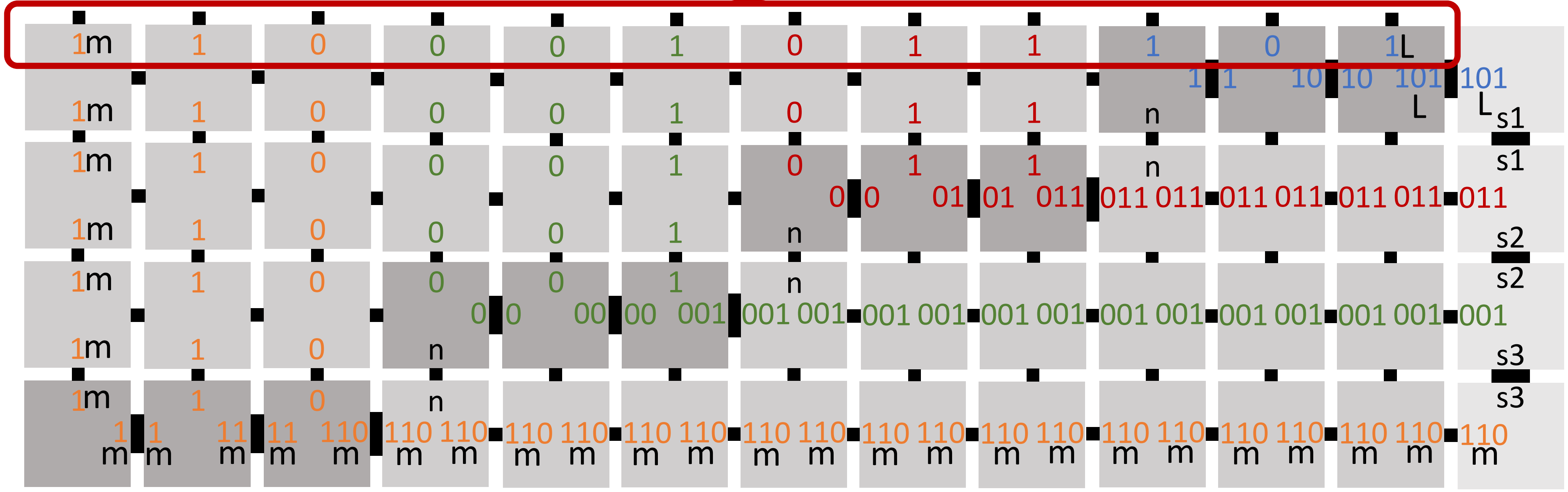

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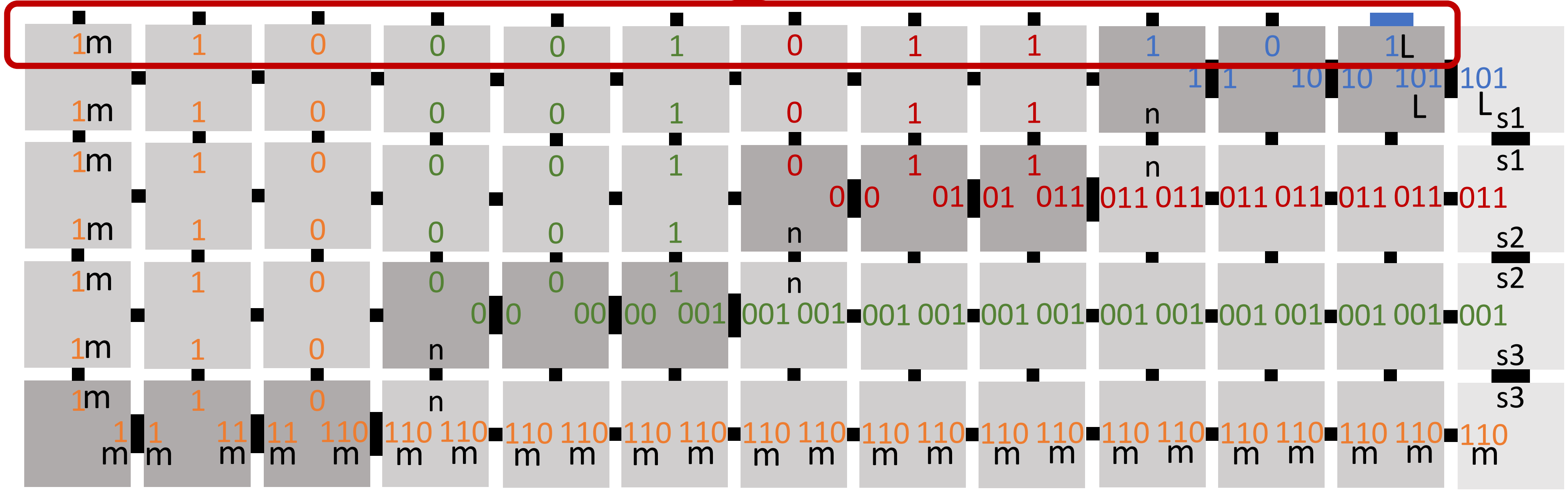

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Formal definition of aTAM

abstract Tile Assembly Model (aTAM), formal definition

- Fix a finite alphabet Σ. A **glue** is a pair $g = (\ell,s) \in \Sigma^* \times \mathbb{N}$, with **label** ℓ and **strength** s.

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  - Define unit vectors N = (0,1), S = (0,–1), E = (1,0), W = (–1,0)
  - For $d \in$ {N, E, S, W}, let d^* denote the **opposite direction** of d, i.e., N* = S, S* = N, E* = W, W* = E.
  - Let t[N], t[E], t[S], t[W] be the glues of t in order.
  - T denotes the set of tile types.
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Sometimes we write $\alpha \to^\Theta \beta$ to emphasize this is with respect to a particular tile system Θ.

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- We say that **α produces β** (in 0 or more steps), denoted $\alpha \rightarrow \beta$, if there is an assembly sequence $\alpha_0, \alpha_1, \ldots$ of length $k \in \mathbb{N} \cup \{\infty\}$ such that
  - $\alpha = \alpha_0$
  - for all $0 \leq i < k$, $\alpha_i \sqsubseteq \beta$, and
  - $S_\beta = \bigcup_i S_{\alpha_i}$
- We say β is the **result** of the assembly sequence.

Why can't we just say $\rightarrow$ is the reflexive, transitive closure $\rightarrow_1^*$ of $\rightarrow_1$?

Sometimes we write $\alpha \rightarrow^\Theta \beta$ to emphasize this is with respect to a particular tile system Θ.

abstract Tile Assembly Model (aTAM), formal definition

- Given assemblies $\alpha,\beta: \mathbb{Z}^2 \dashrightarrow T$, we say α is a **subassembly** of β, written $\alpha \sqsubseteq \beta$ if
  - $S_\alpha \subseteq S_\beta$ (*α is contained in* β), and
  - for all $p \in S_\alpha$, $\alpha(p) = \beta(p)$ (α *and* β *agree on tile types wherever they share a position*)

Question: If $\alpha \sqsubseteq \beta$, can α grow into β?

- We say $\Theta = (T,\sigma,\tau)$ is a **tile system**, where T is a finite set of tile types, $\tau \in \mathbb{N}^+$ is the **temperature**, and $\sigma: \mathbb{Z}^2 \dashrightarrow T$ is the finite, τ-stable **seed assembly**.
- We say **α produces β in one step**, denoted $\alpha \to_1 \beta$, to denote that $\alpha \sqsubseteq \beta$, $|S_\beta \setminus S_\alpha| = 1$, and letting $\{p\} = S_\beta \setminus S_\alpha$ be the point in β but not α, the cut $(\{p\},S_\alpha)$ of the binding graph B_β has weight $\geq \tau$.
  - (*one new tile* $\beta(p)$ *attaches to* α *with strength at least* τ *to create* β)
  - If the tile type added is t, write $\beta = \alpha + (p \mapsto t)$.
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- We say β is the **result** of the assembly sequence.
- If k is finite, it is routine to verify that $\beta = \alpha_k$, and $\to$ is the reflexive, transitive closure $\to_1^*$ of $\to_1$.

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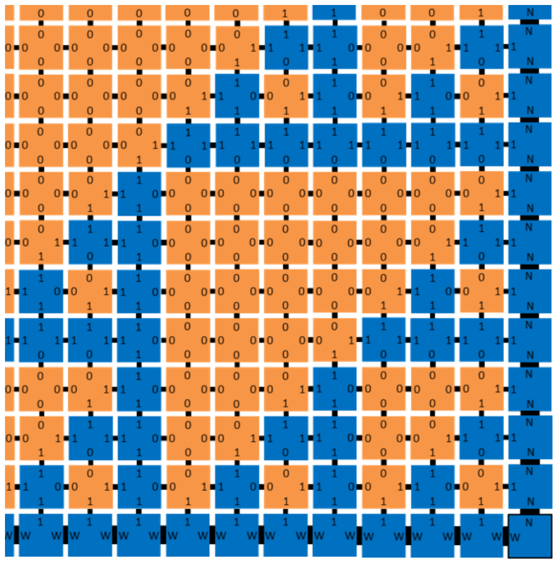

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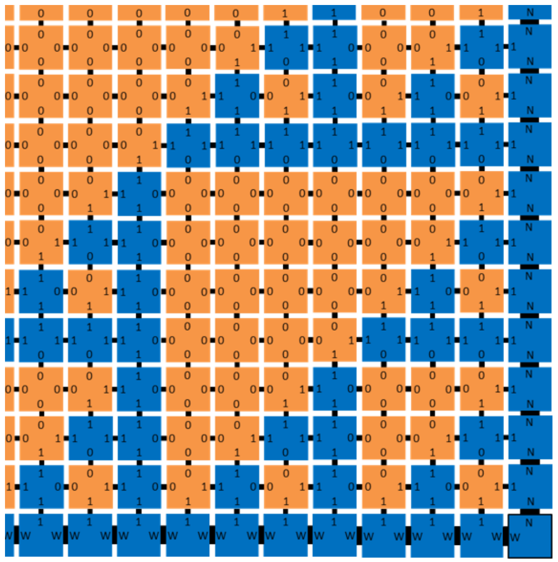

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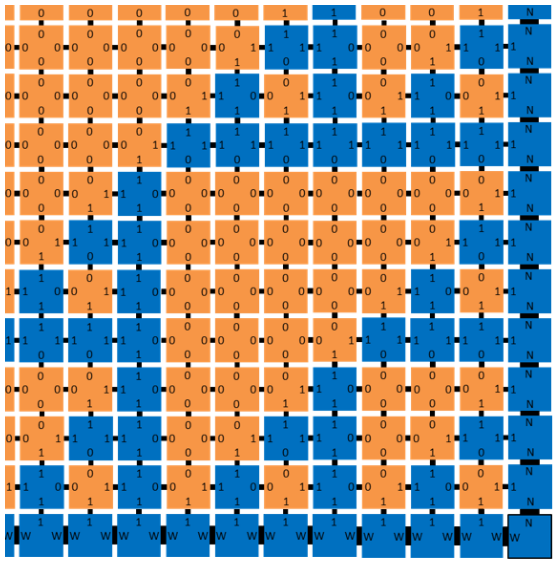

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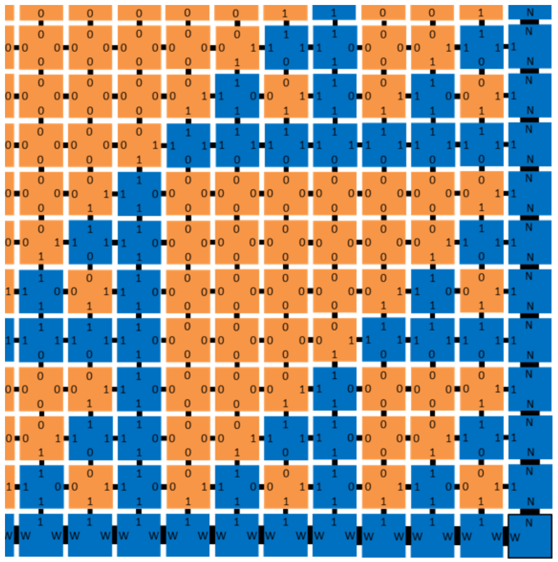

Basic stability result

Observation: Let $\alpha \sqsubseteq \beta$ be stable assemblies and $p \in \mathbb{Z}^2 \setminus S_\beta$ such that $\alpha + (p{\mapsto}t)$ is stable. Then $\beta + (p{\mapsto}t)$ is also stable.

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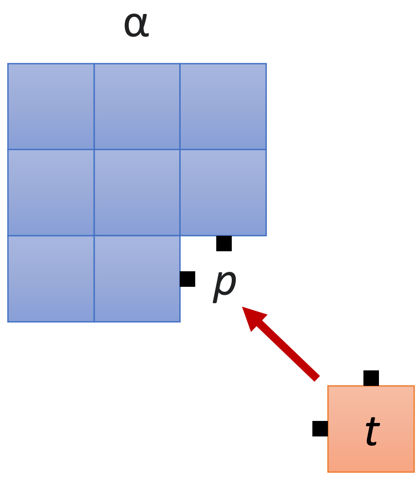

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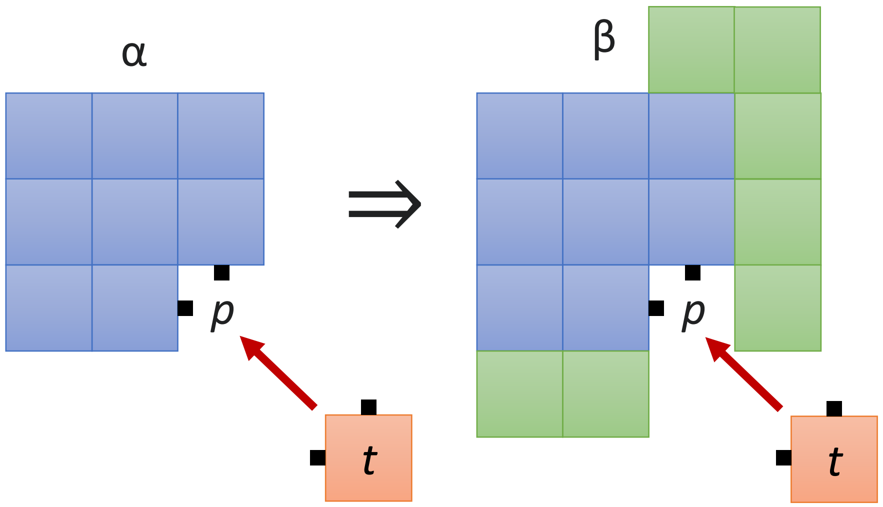

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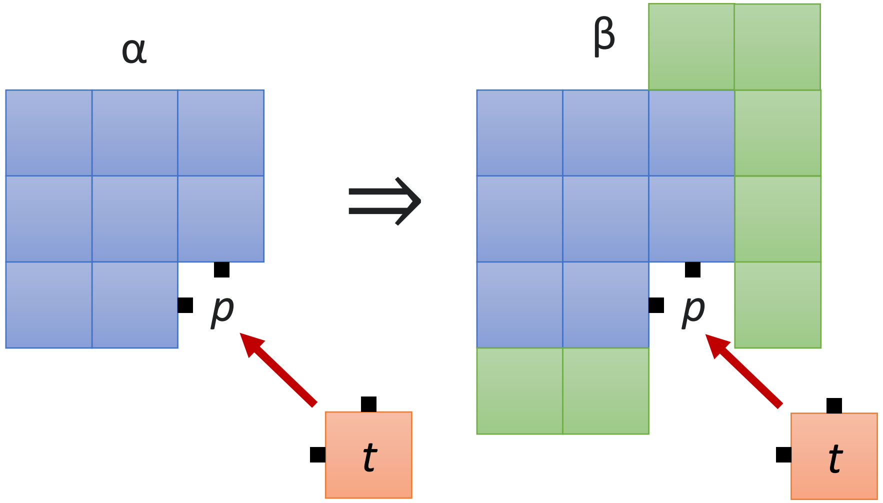

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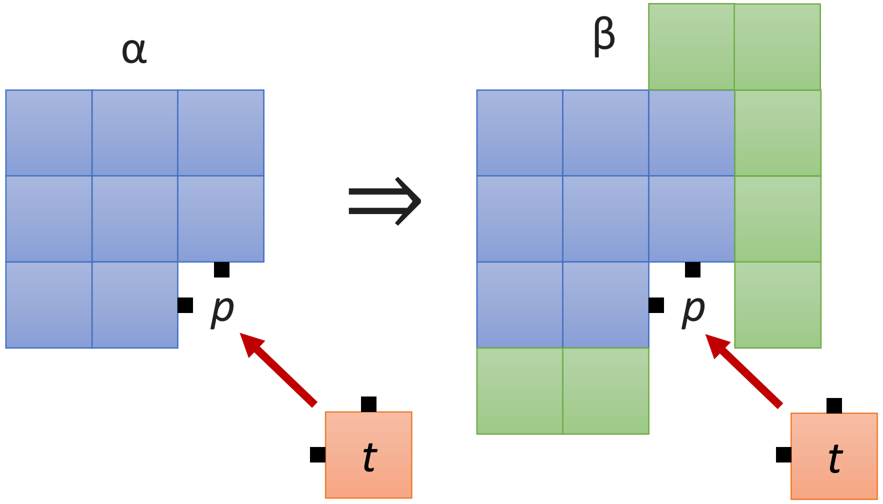

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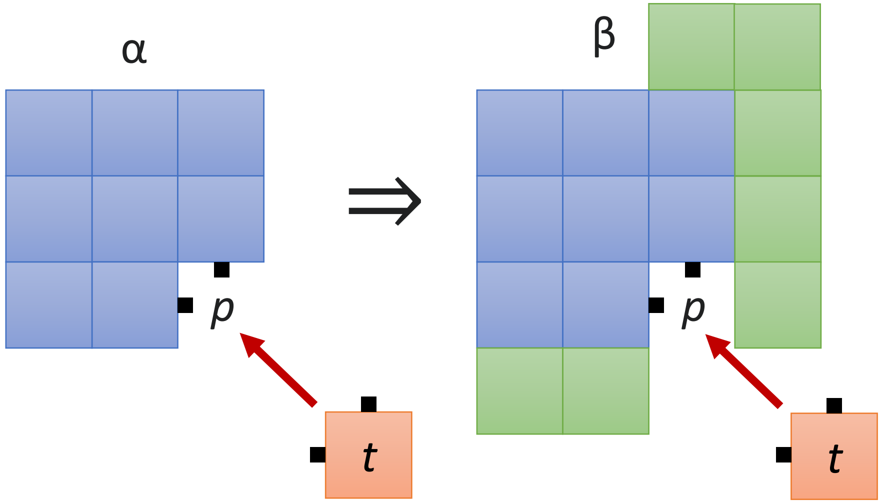

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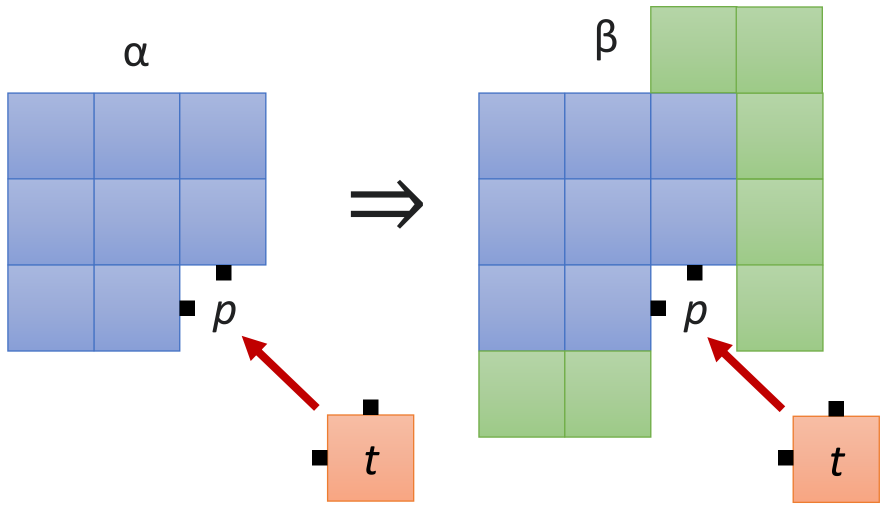

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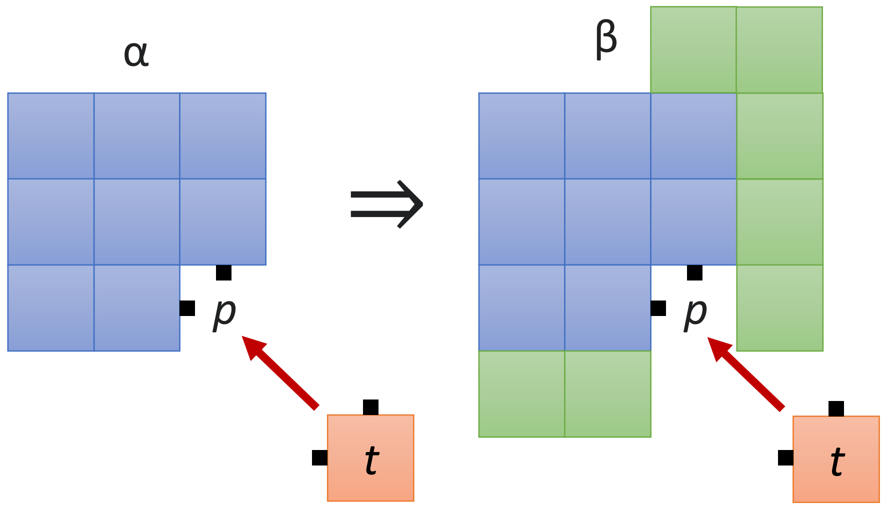

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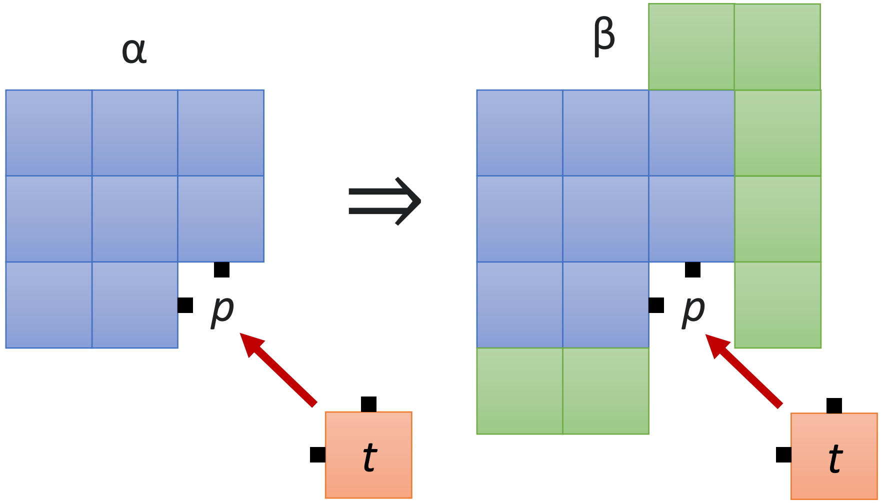

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   4. so the cut (t, S_β) is also stable. **QED**

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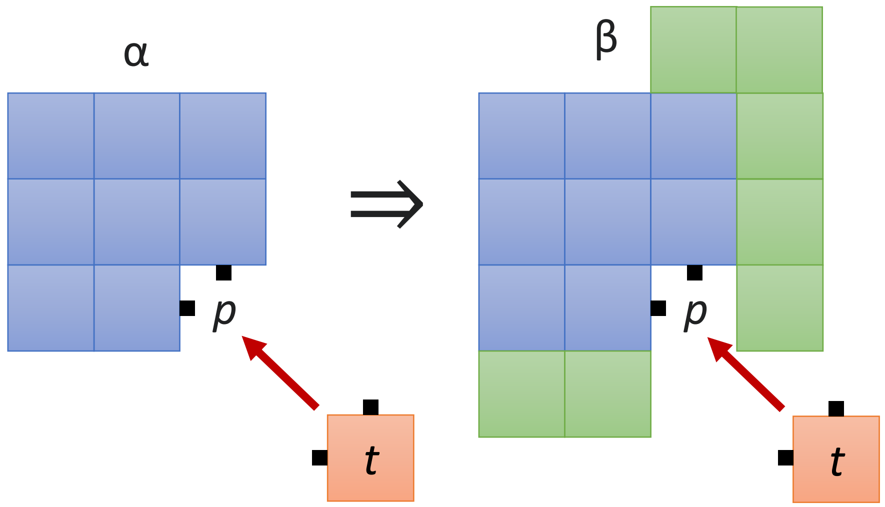

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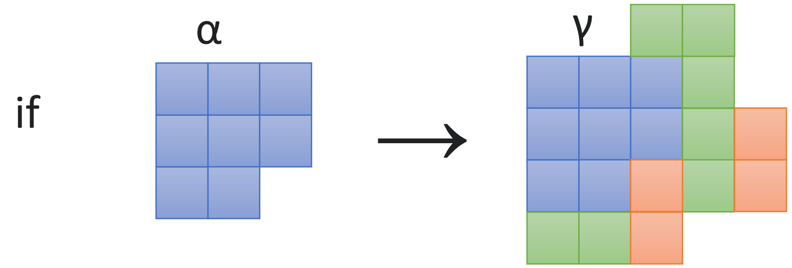

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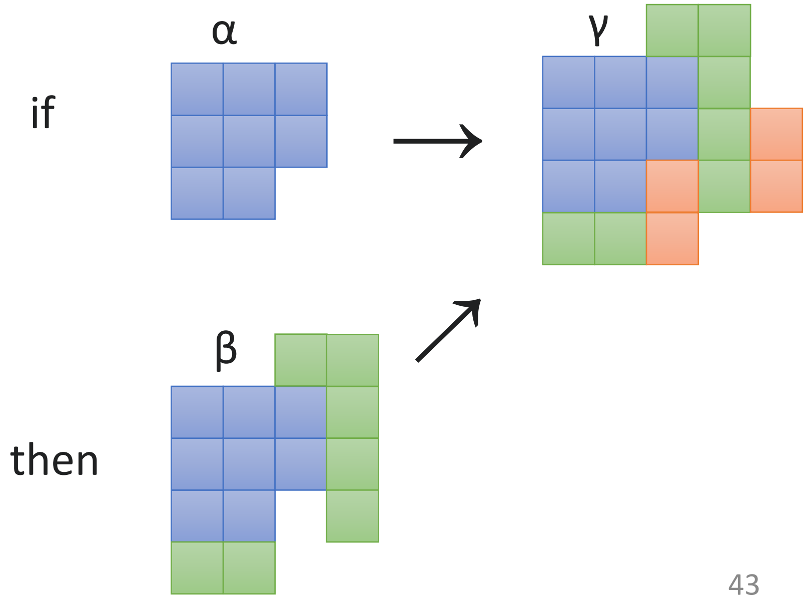

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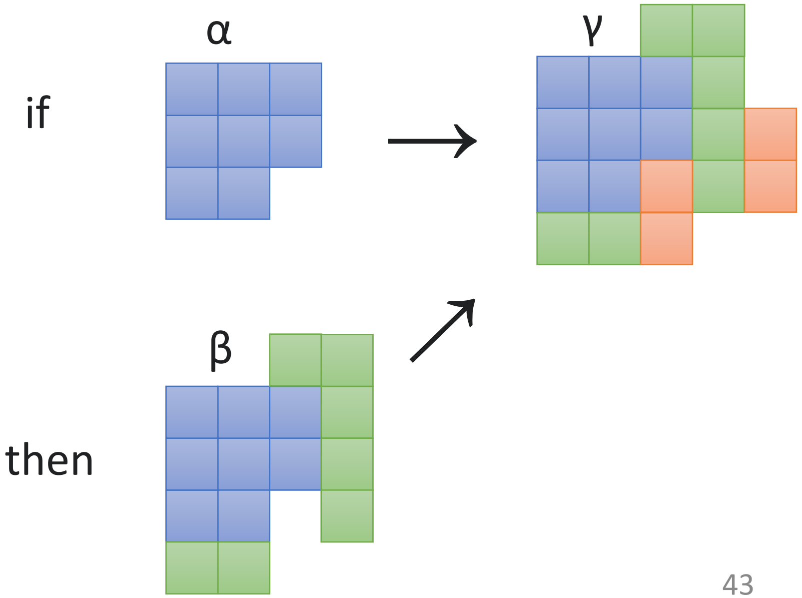

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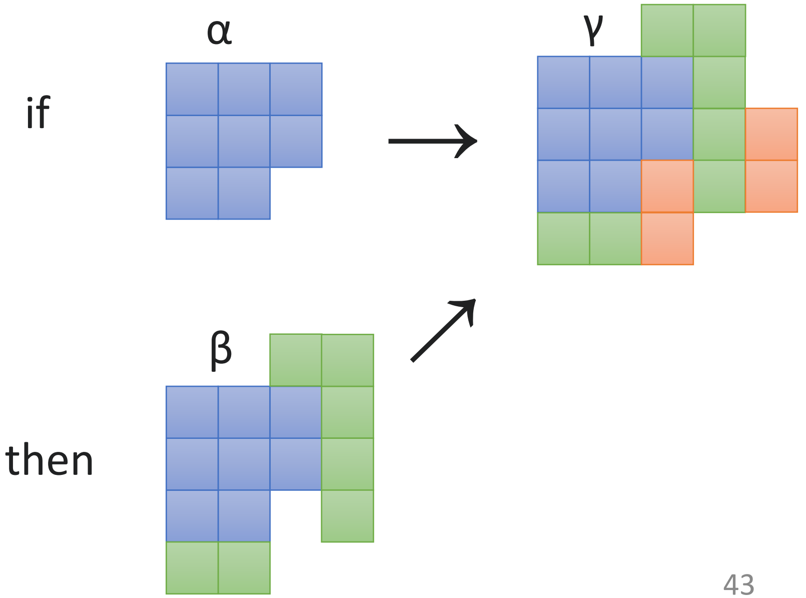

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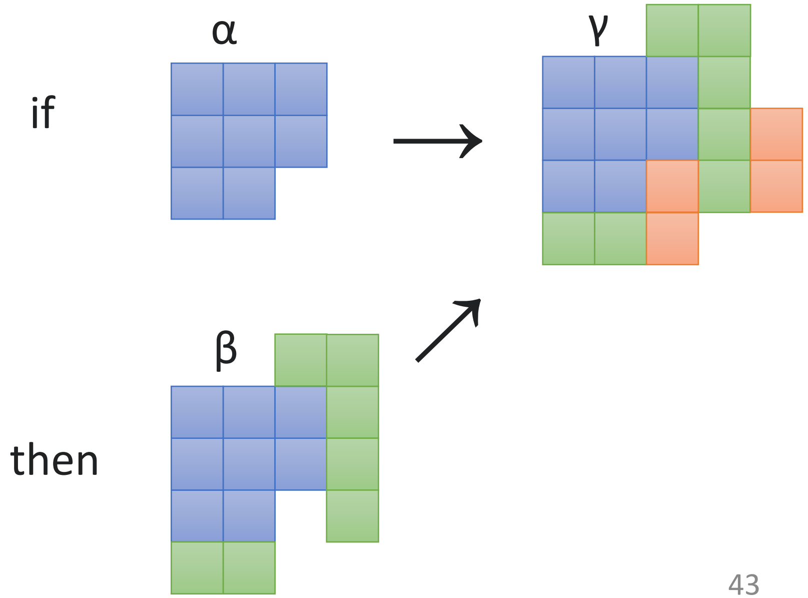

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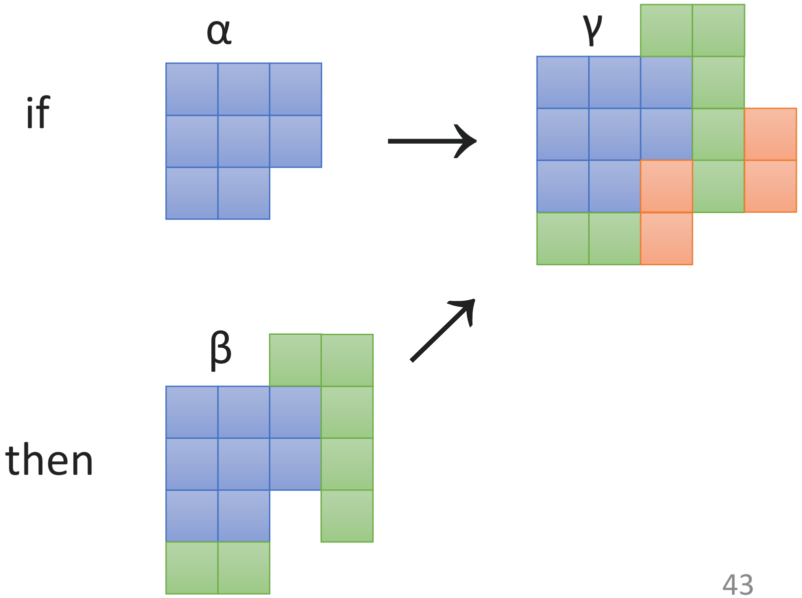

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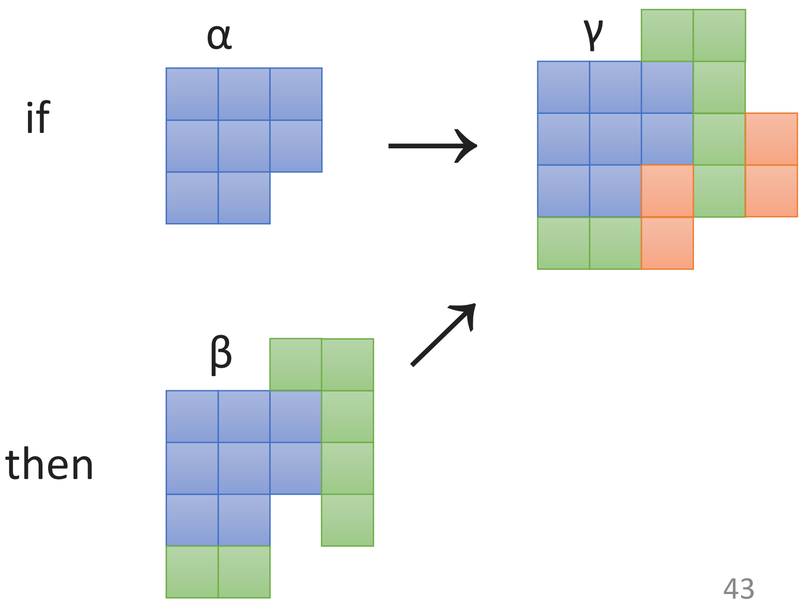

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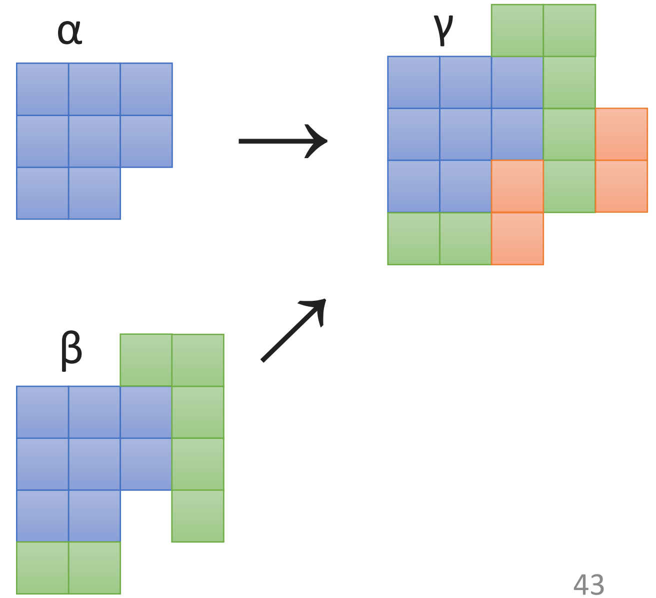

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5. Then for each j, $\alpha_{i(j)} \sqsubseteq \beta_j$, so previous Observation implies that $\beta_j + (p_{i(j)} \mapsto t_{i(j)})$ is stable.
6. Thus the assembly sequence is valid (each tile attachment is stable), showing $\beta \to \gamma$. **QED**

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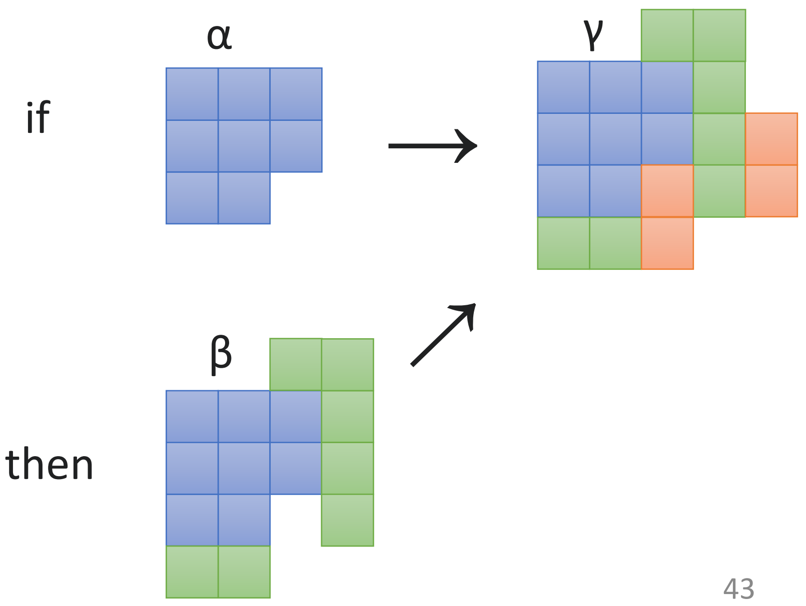

example of usefulness of Rothemund's Lemma

- Recall two alternate characterizations of deterministic tile systems:
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- Rothemund's Lemma can be used to show that (b) implies (a)
  - will skip in lecture (optional problem on homework 1)

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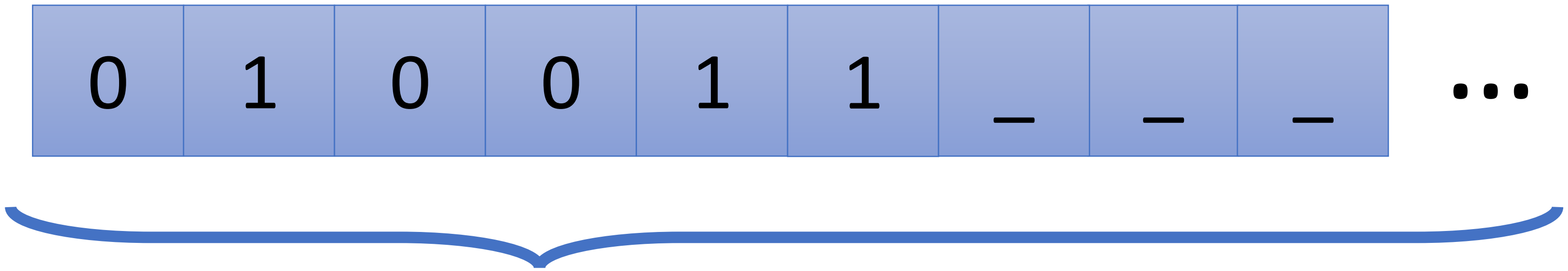
Concrete example of simulation algorithm creating a fair assembly sequence?

How computationally powerful are self-assembling tiles?

Turing machines

Turing machines



tape ≈ memory

Turing machines

state ≈ line of code

$$\underbrace{\boxed{0}\boxed{1}\boxed{0}\boxed{0}\boxed{1}\boxed{1}\boxed{\_}\boxed{\_}\boxed{\_}\ \cdots}_{\textit{tape} \,\approx\, \text{memory}}$$

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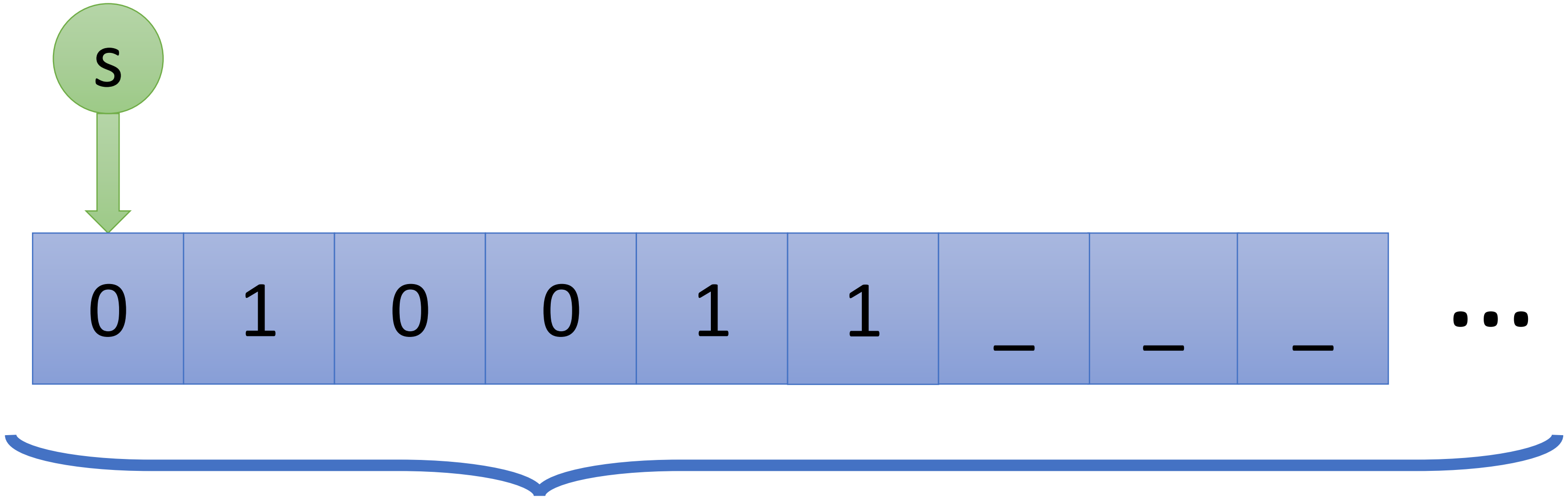

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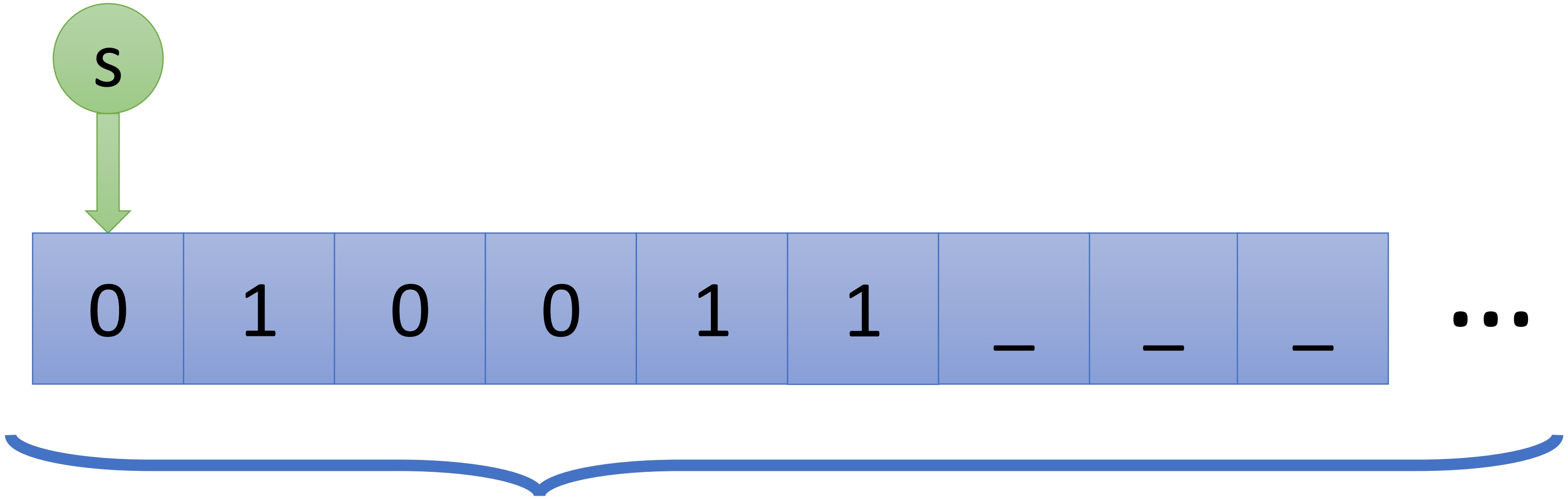

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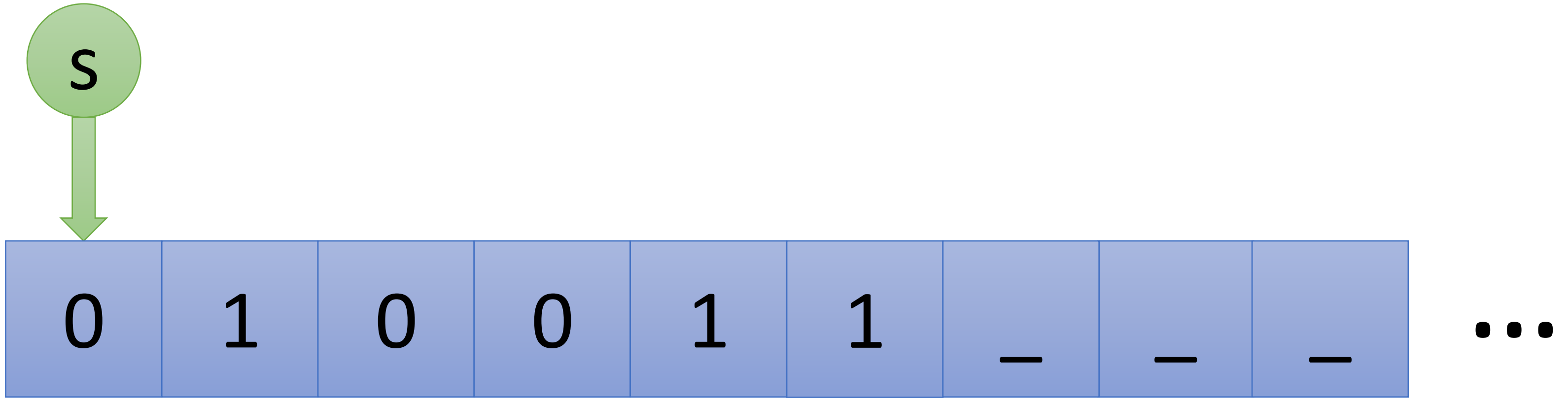

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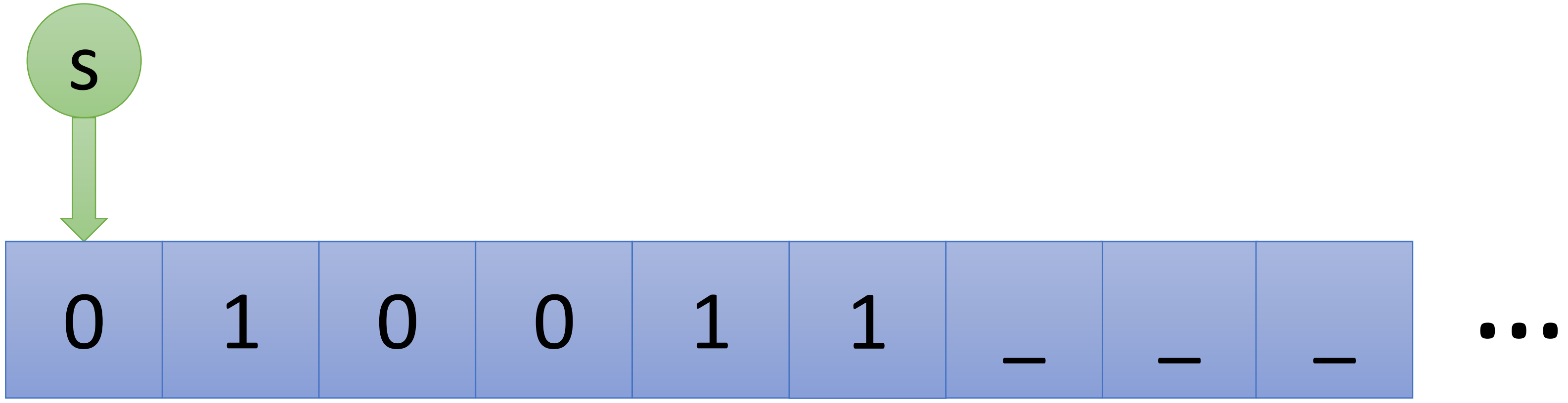

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Turing machines

state ≈ line of code

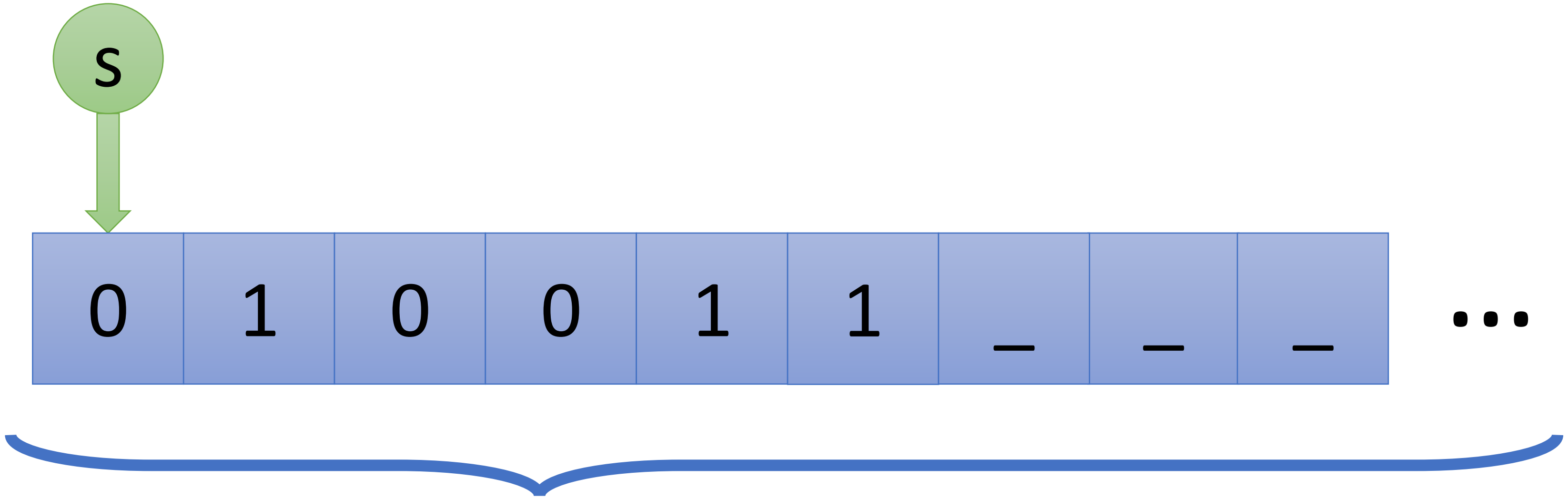
initial state = s

current symbol

current state

next state

s,0: q,0,→



transitions

(instructions)

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Turing machines

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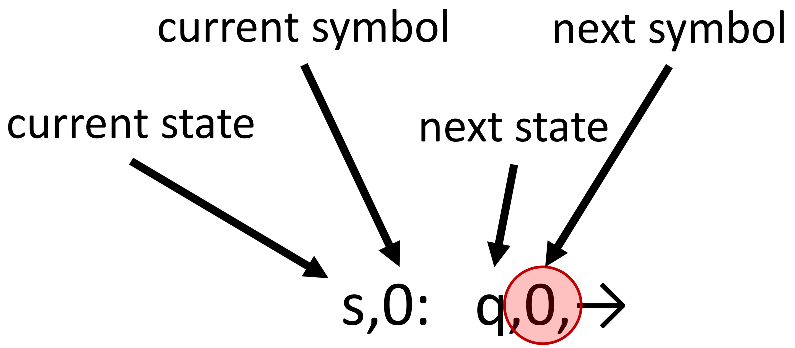
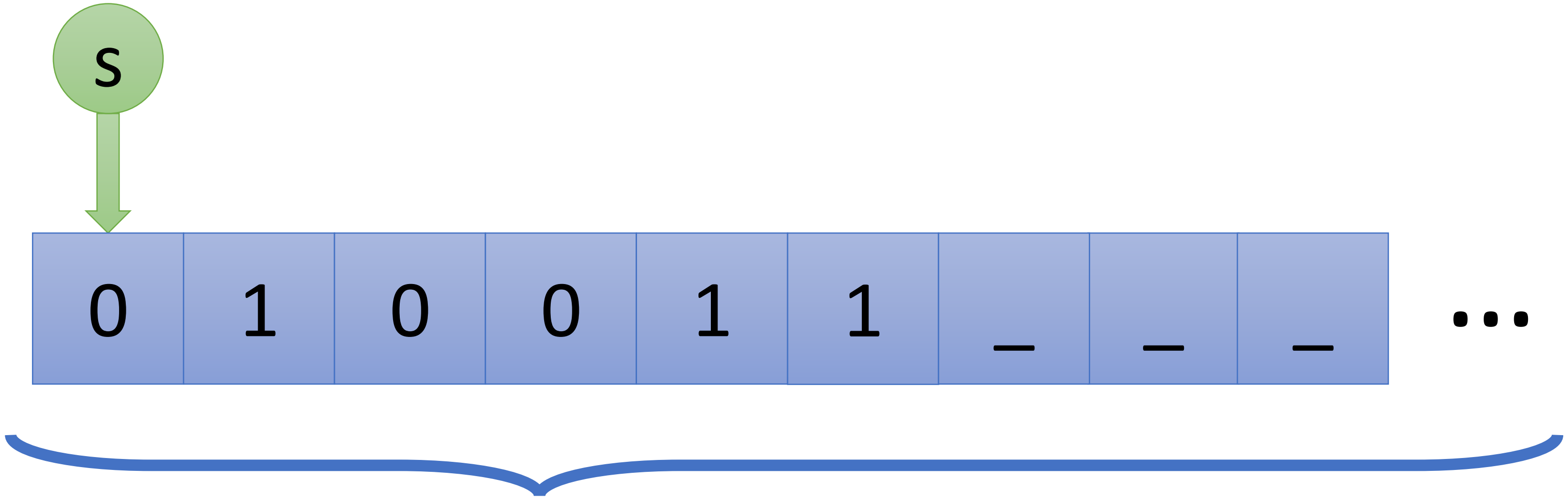
initial state = s



transitions
(instructions)



tape ≈ memory

Turing machines

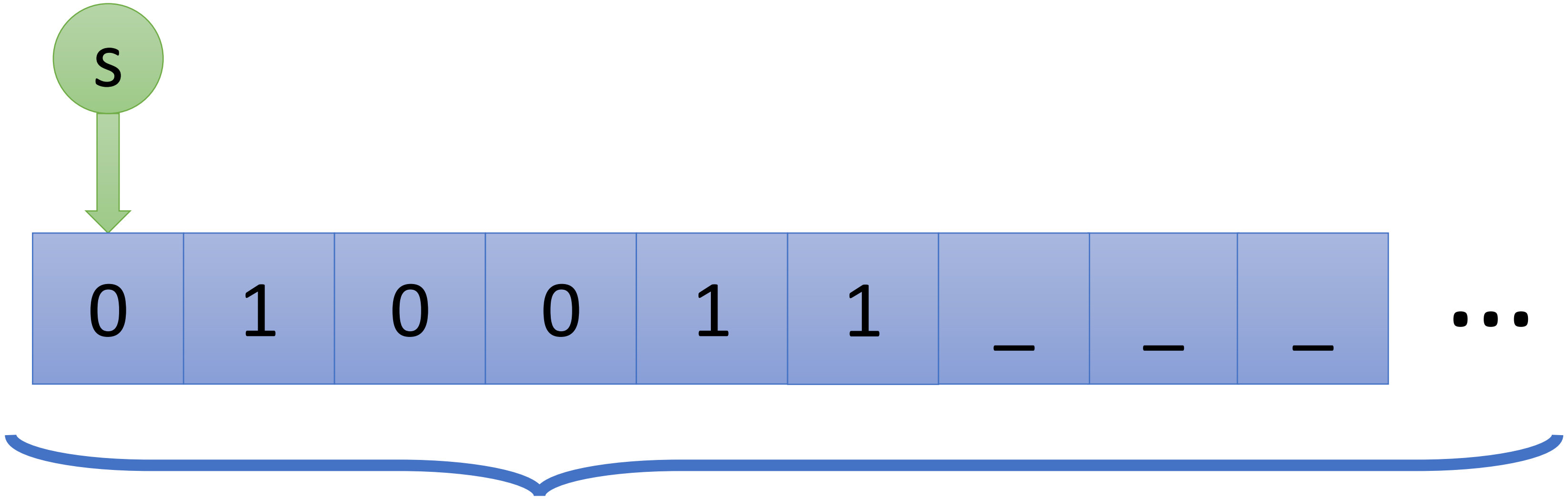
state ≈ line of code

initial state = s

current symbol next symbol

current state next state next move

s,0: q,0,→



transitions

(instructions)

tape ≈ memory

Turing machines

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initial state = s

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s,0: q,0,→

q,0: t,1,←

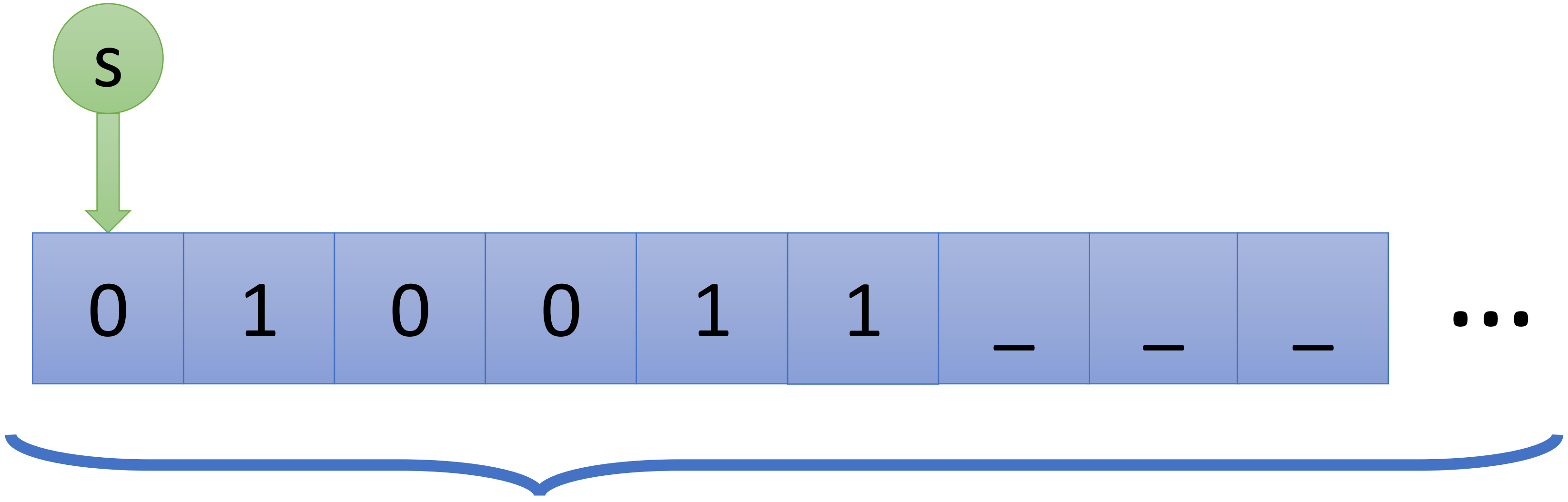
q,1: s,0,→

t,0: u,1,→

u,1: HALT

transitions

(instructions)



tape ≈ memory

Turing machines

state ≈ line of code

initial state = s

current symbol next symbol

current state next state next move

s,0: q,0,→

q,0: t,1,←

q,1: s,0,→

t,0: u,1,→

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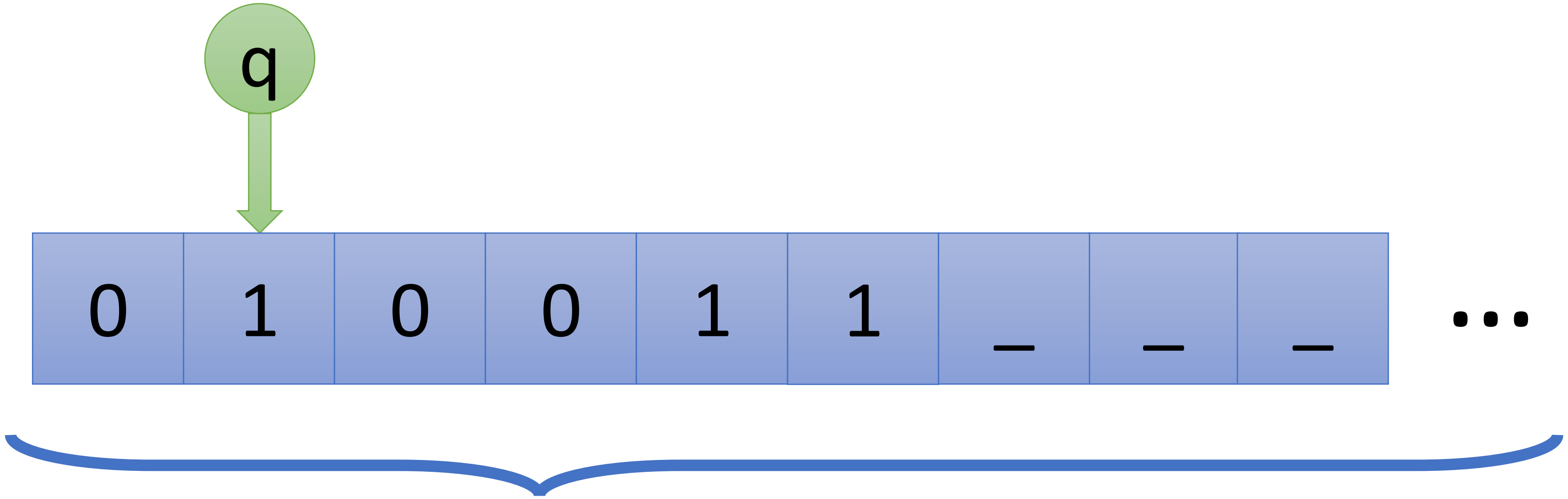
transitions

(instructions)



tape ≈ memory

Turing machines

state ≈ line of code

initial state = s

current state, current symbol, next state, next symbol, next move

s,0:   q,0,→

q,0:   t,1,←

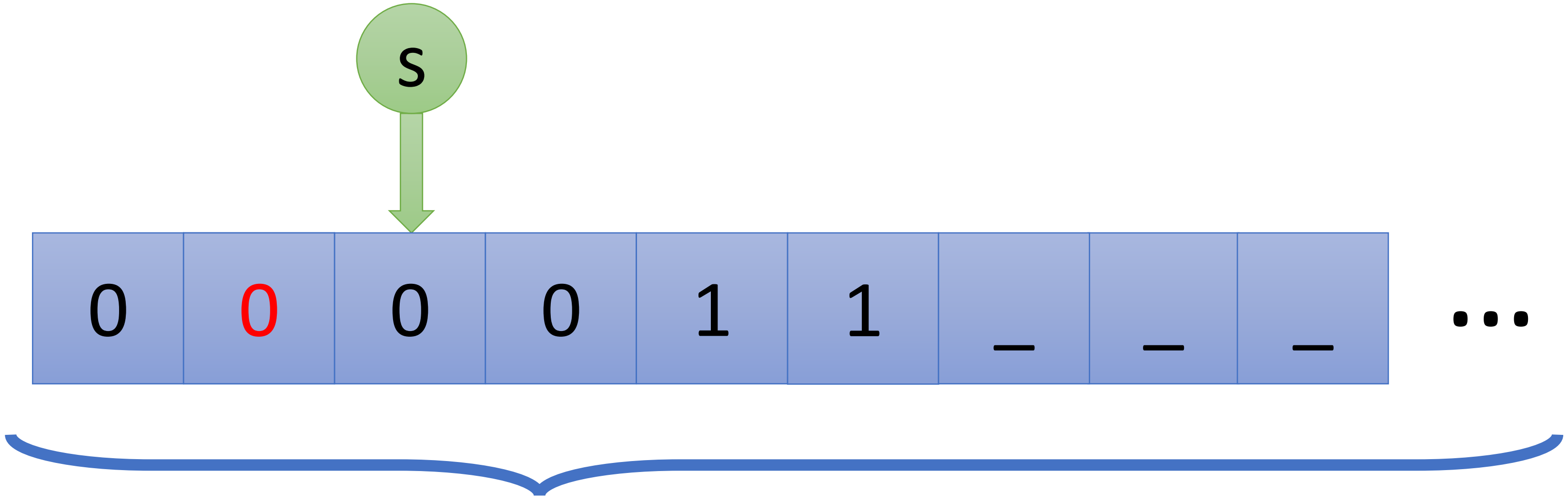
q,1:   s,0,→

t,0:   u,1,→

u,1:   HALT

transitions

(instructions)



tape ≈ memory

Turing machines

current symbol next symbol

current state next state next move

s,0: q,0,→

q,0: t,1,←

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t,0: u,1,→

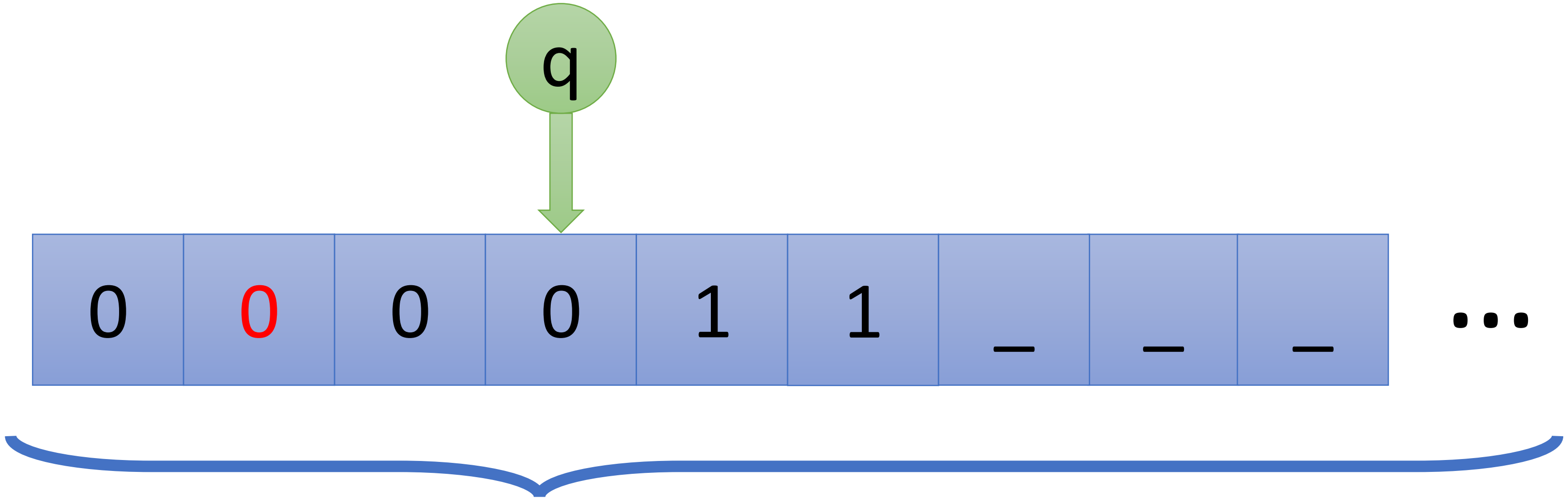
u,1: HALT

transitions

(instructions)

state ≈ line of code

initial state = s



tape ≈ memory

Turing machines

current symbol   next symbol

current state   next state   next move

s,0:   q,0,→

q,0:   t,1,←

q,1:   s,0,→

t,0:   u,1,→

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transitions

(instructions)

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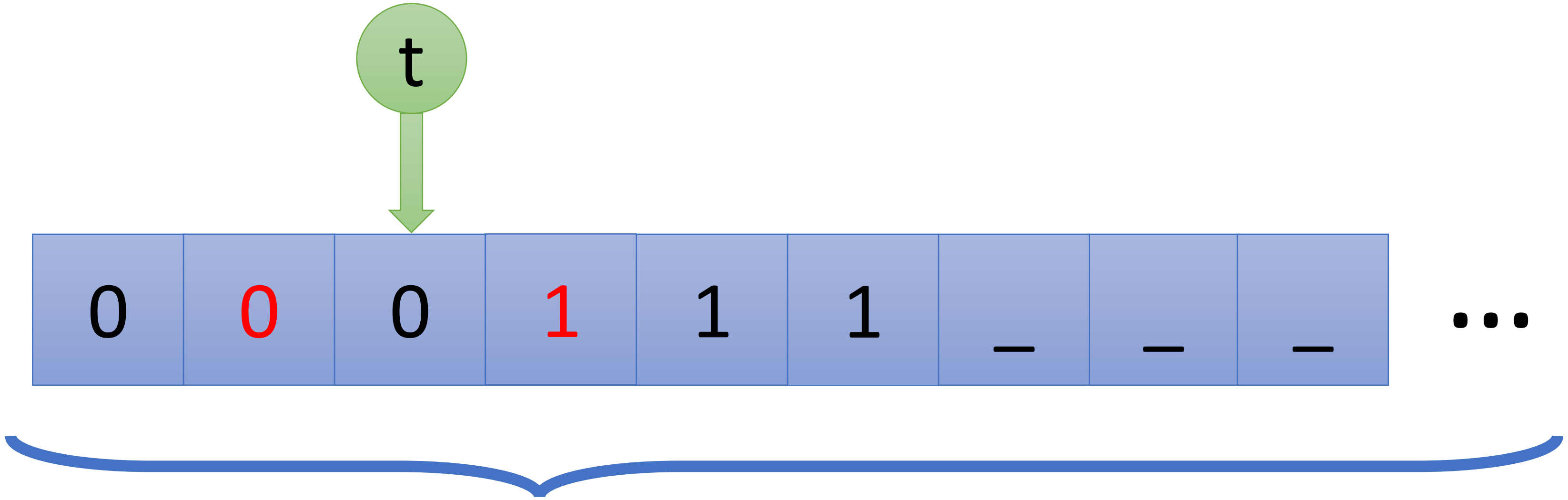

tape ≈ memory

Turing machines

state ≈ line of code

initial state = s

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s,0:   q,0,→

q,0:   t,1,←

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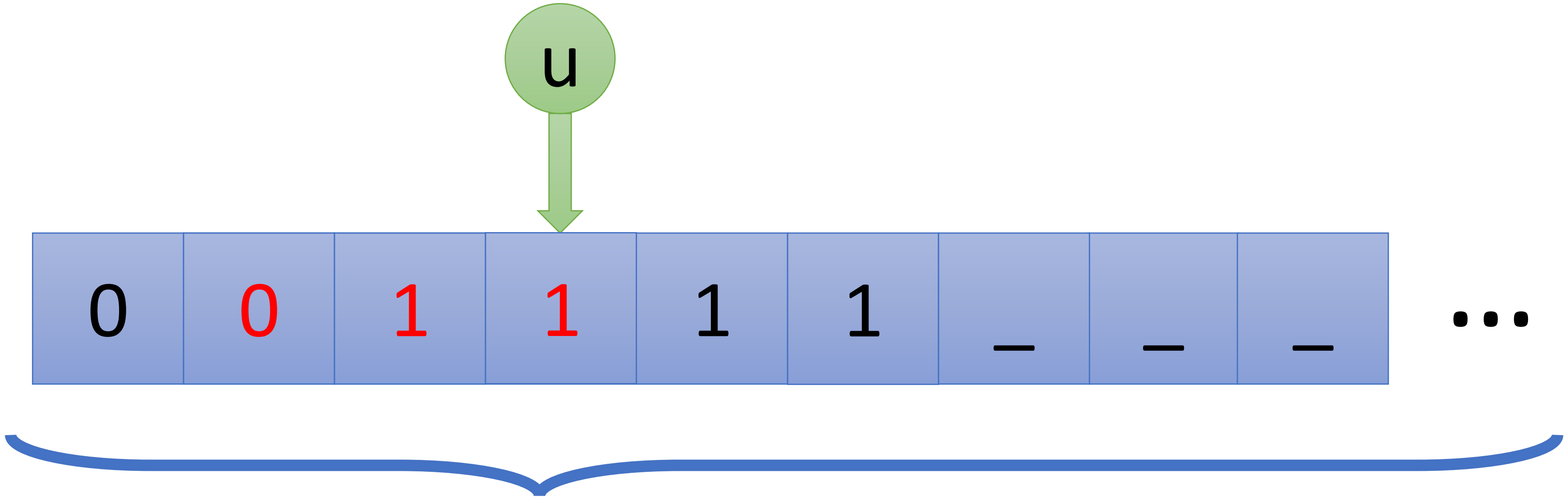
transitions

(instructions)



tape ≈ memory

Tile assembly is Turing-universal

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s,0: q,0,→

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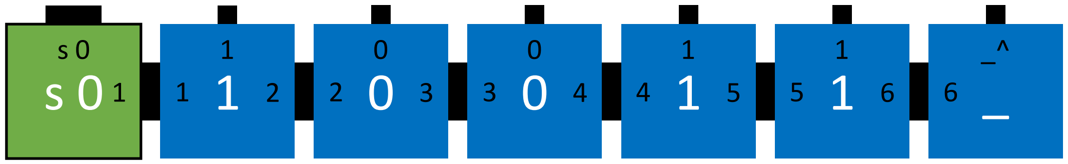

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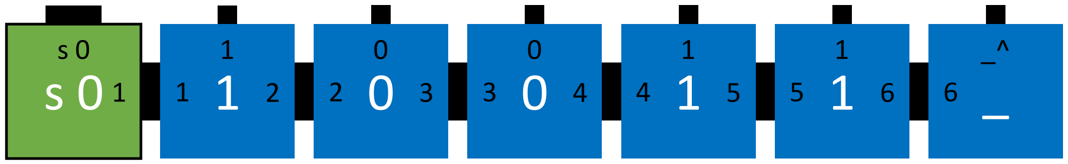

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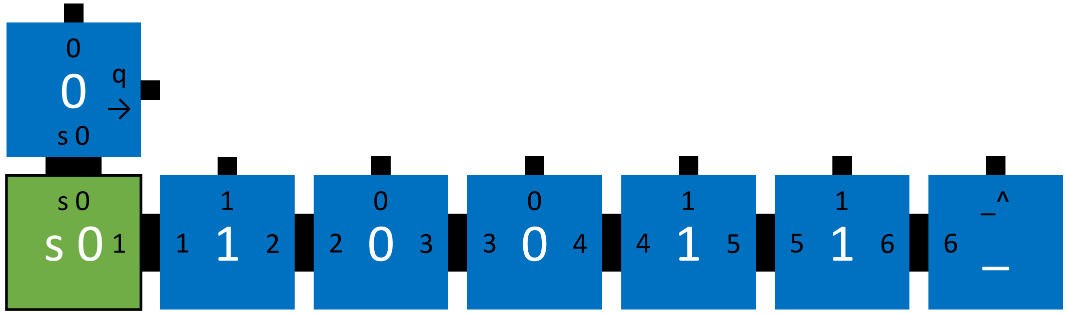

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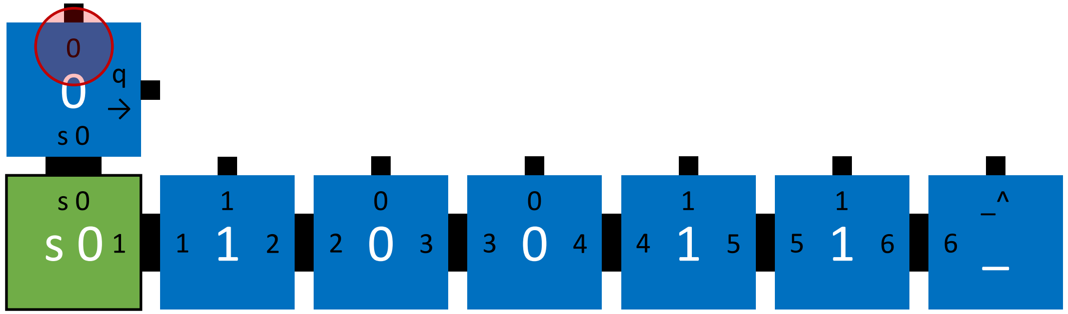

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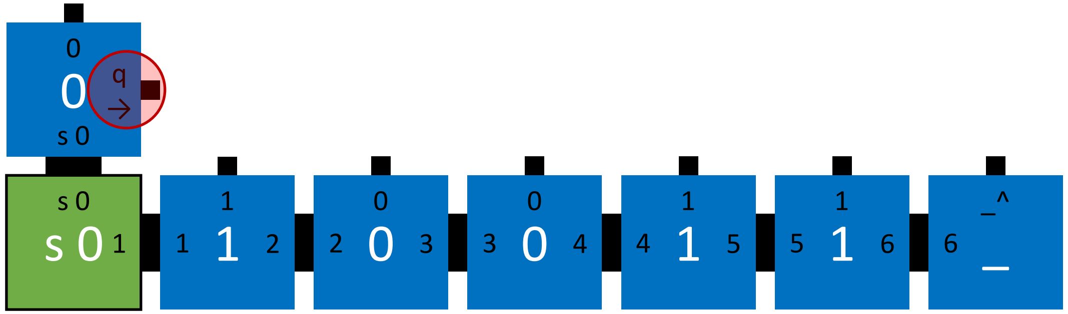

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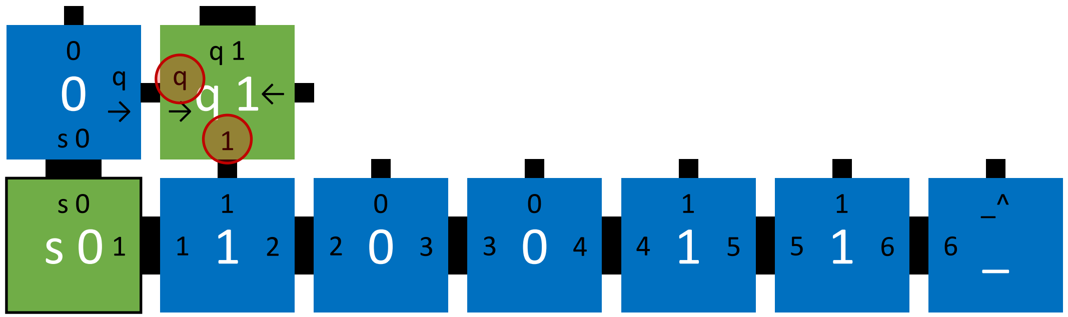

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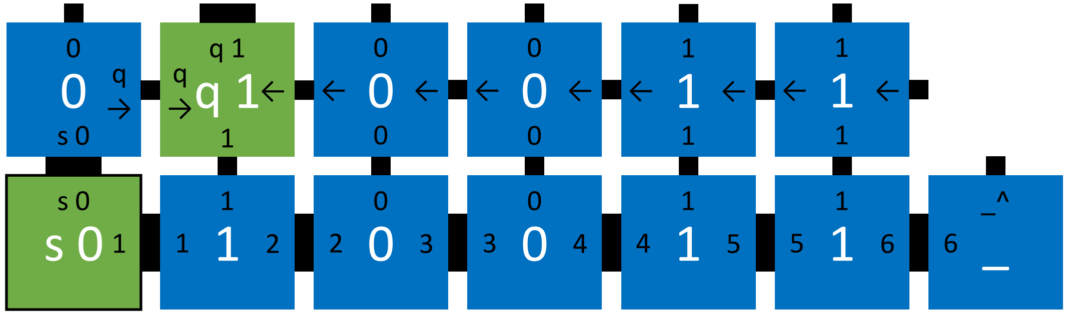

s,0: q,0,→

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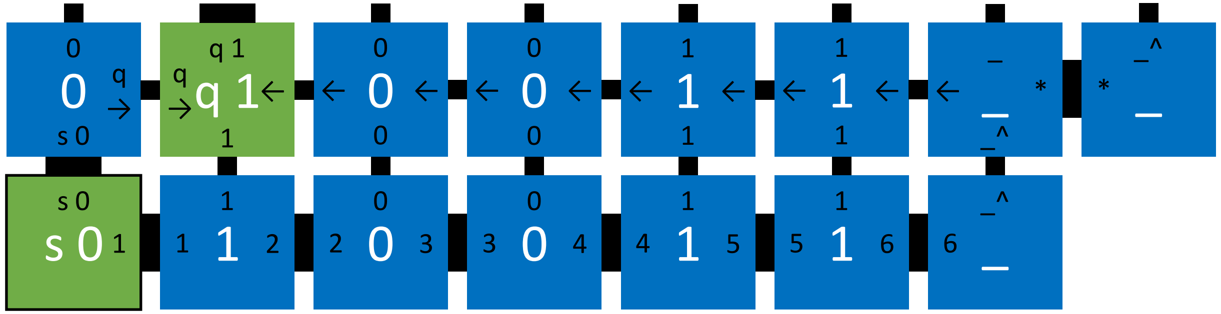

s,0: q,0,→

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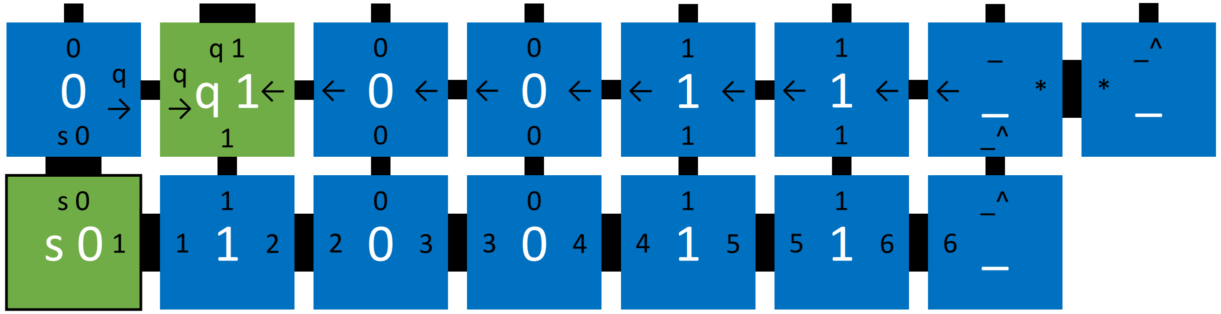

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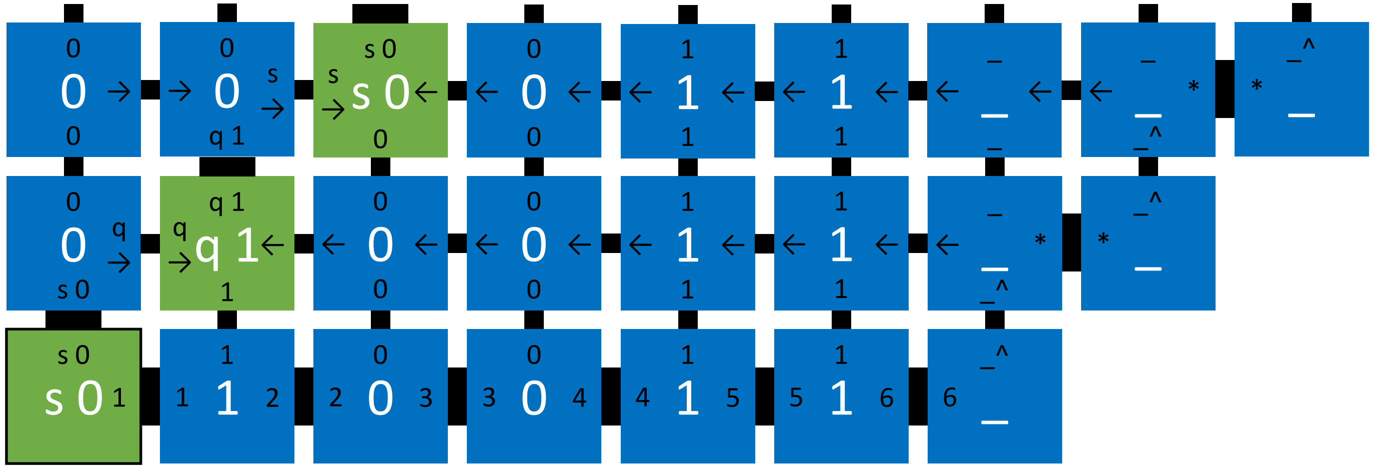

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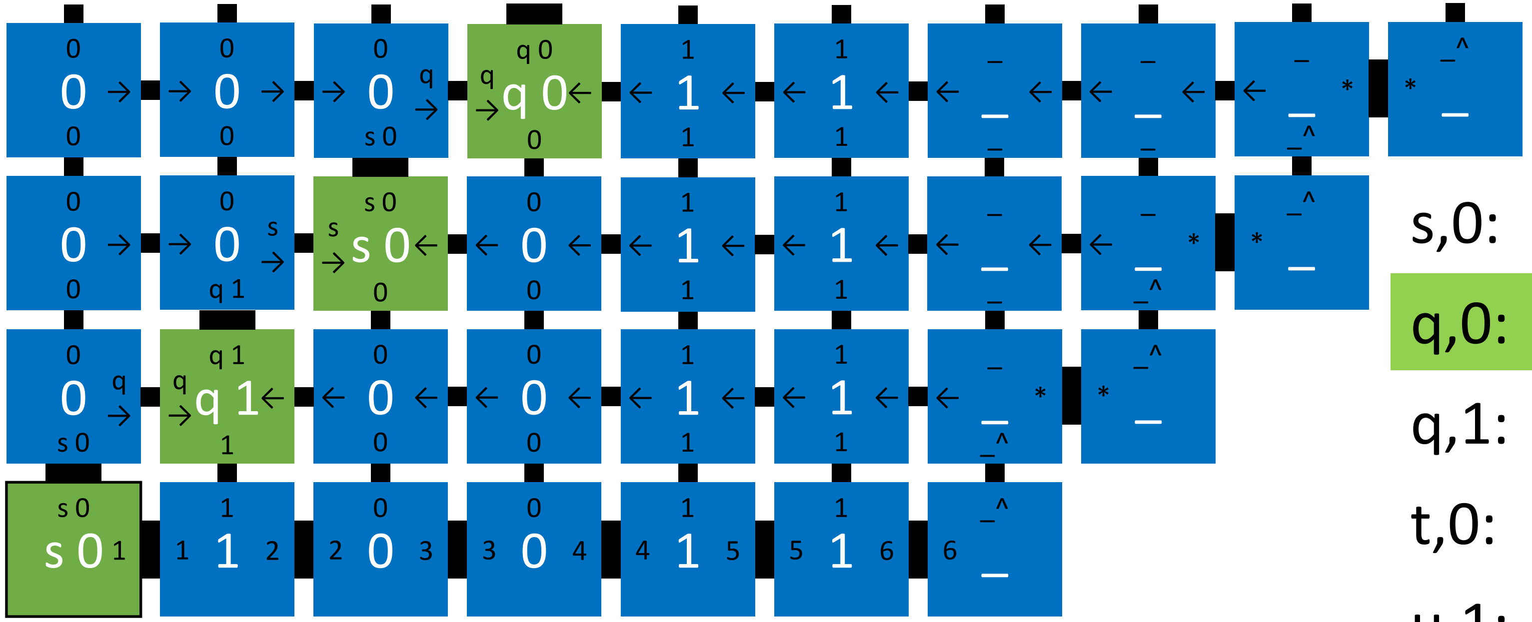

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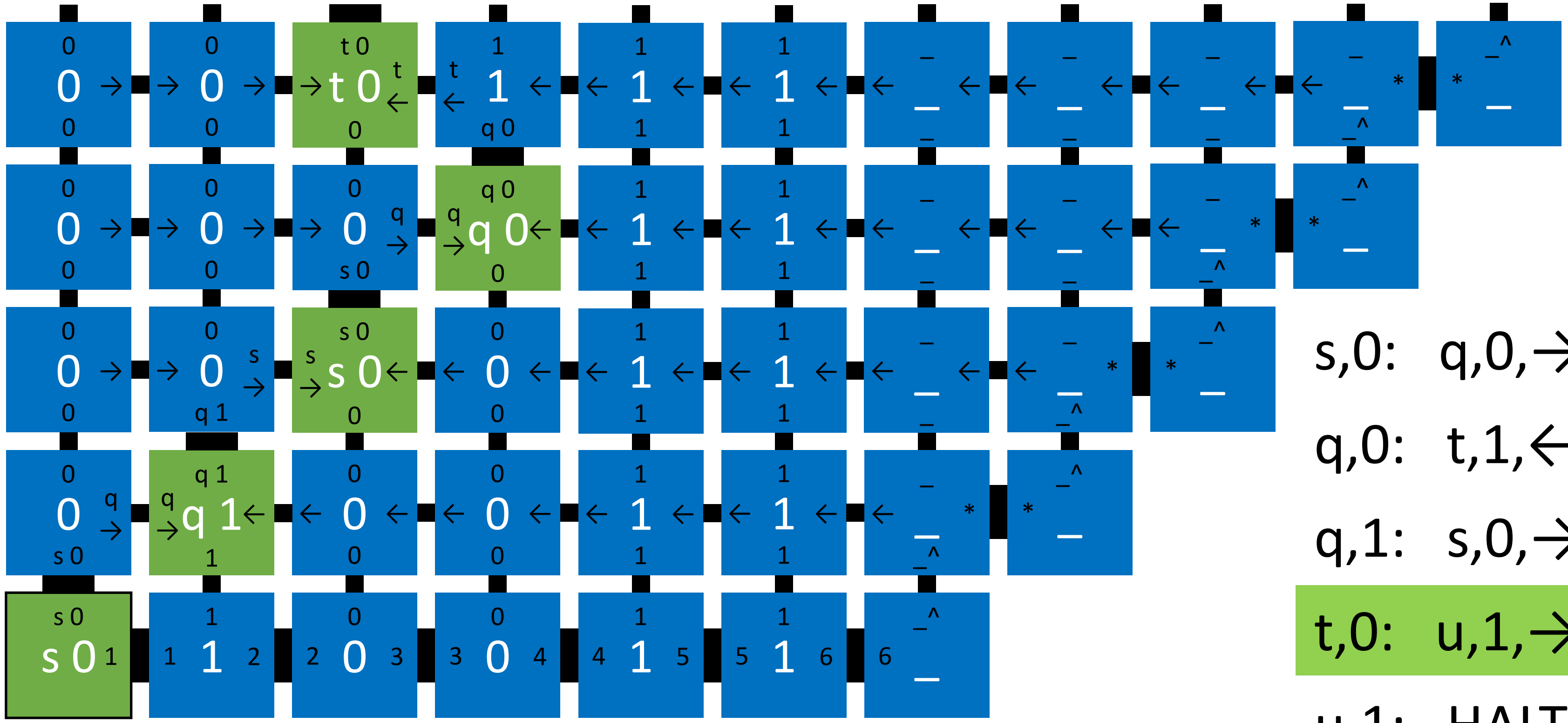

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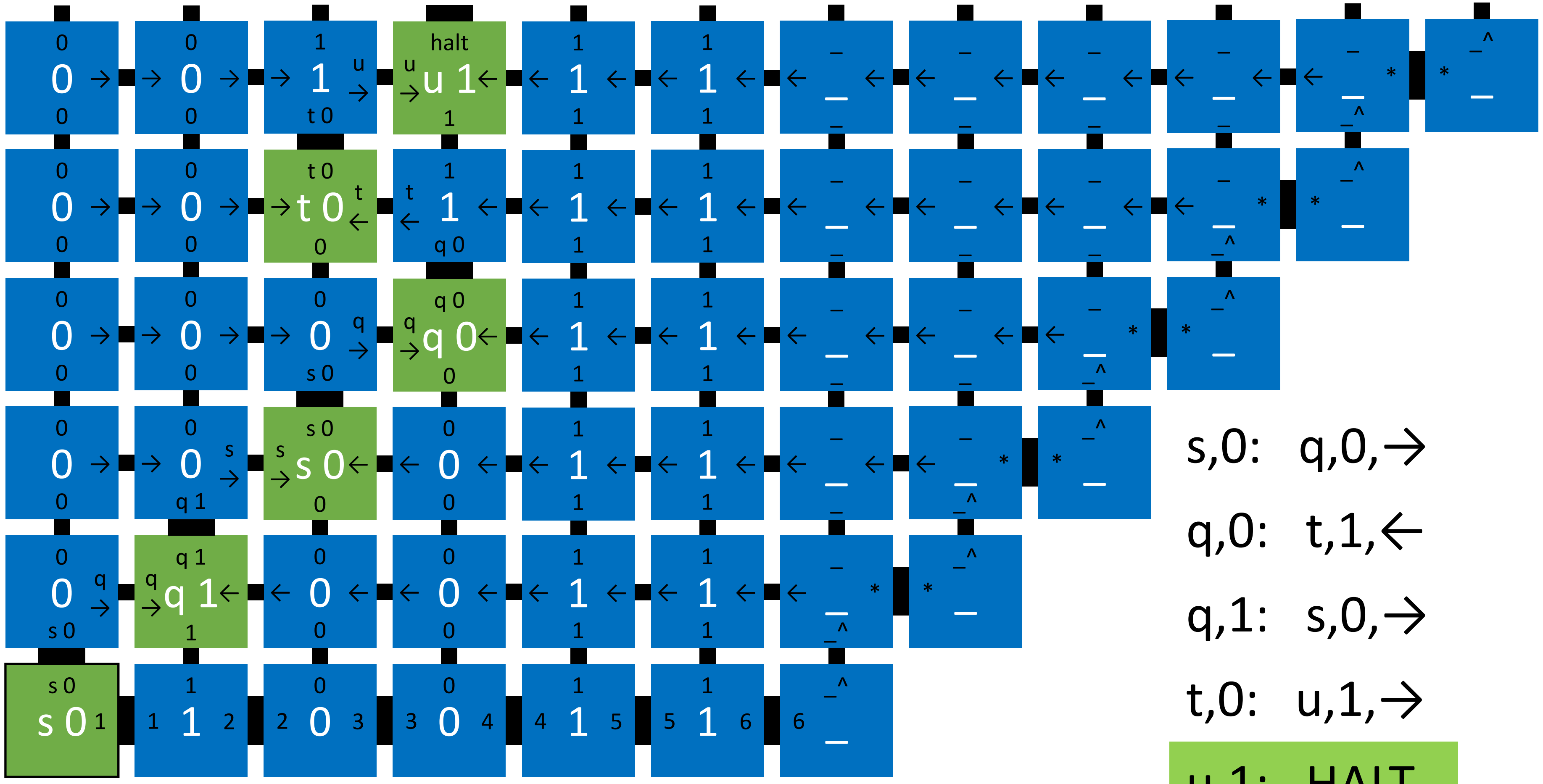

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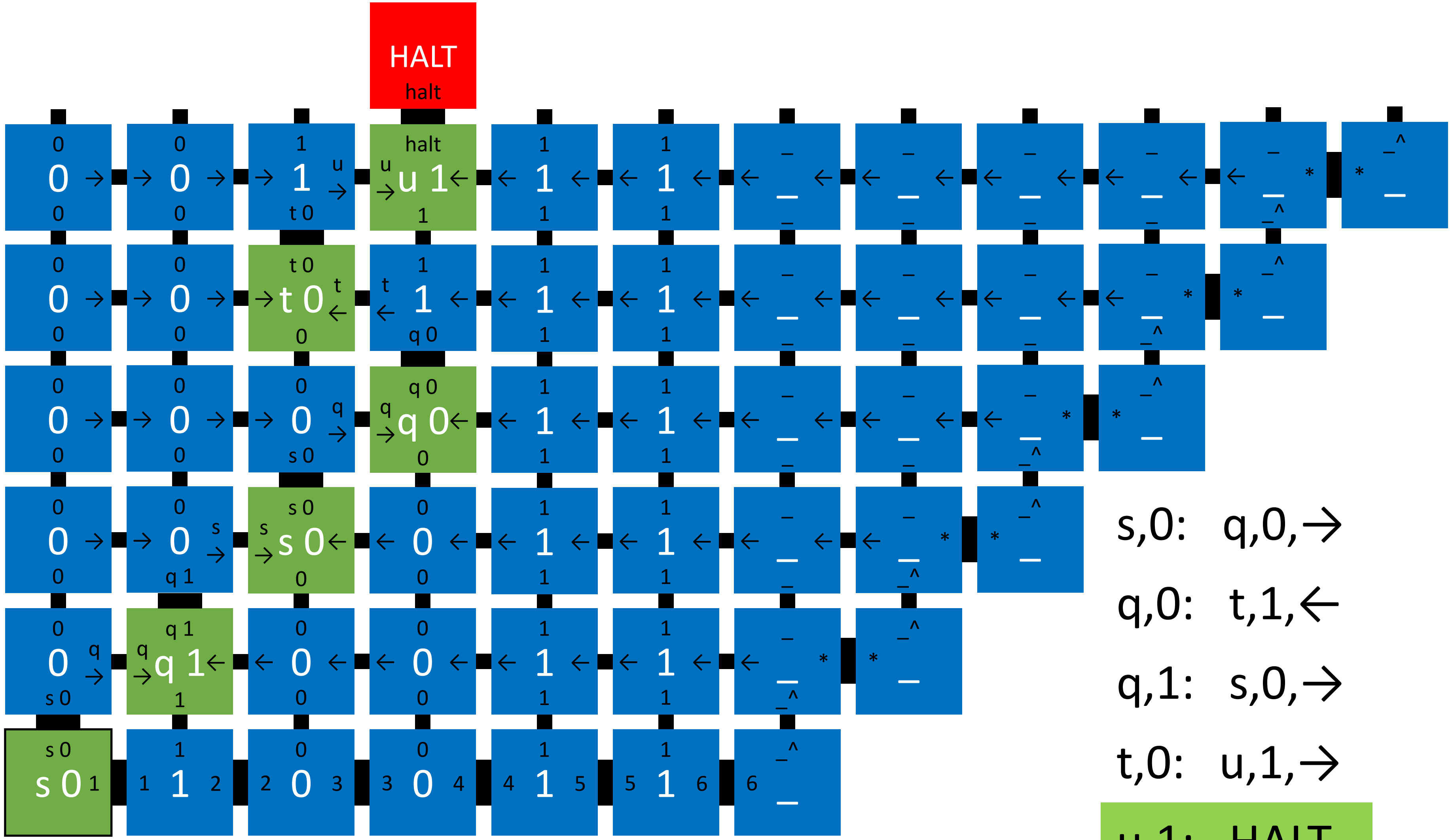

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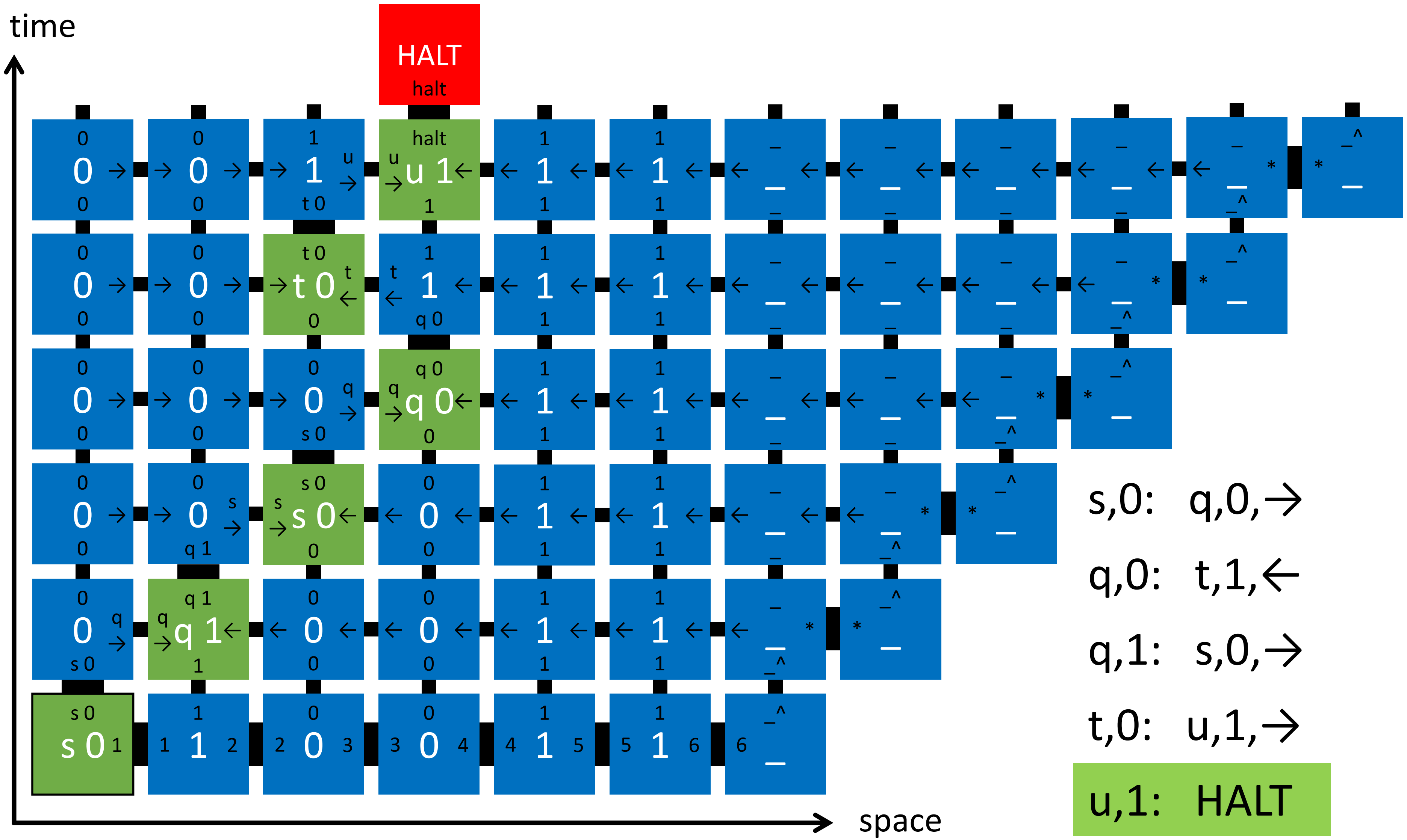

s,0: q,0,→

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Complexity of self-assembled shapes

- We've seen how use algorithmic tiles to:
  - self-assemble n x n squares with "few" tile types $O(\log n / \log \log n)$
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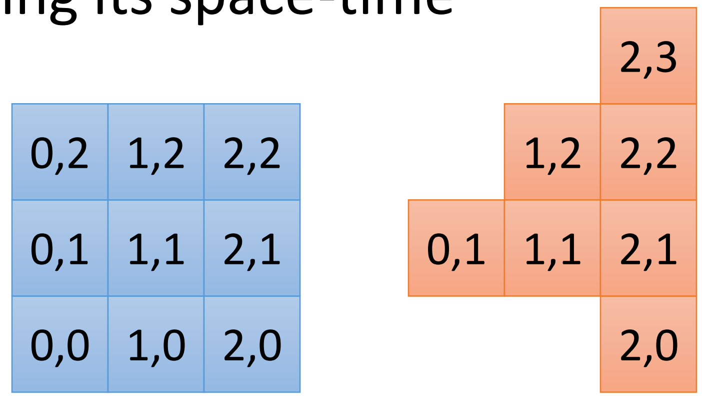
  - Define a shape to be a finite, connected subset of $\mathbb{N}^2$.



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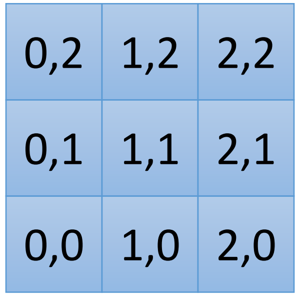

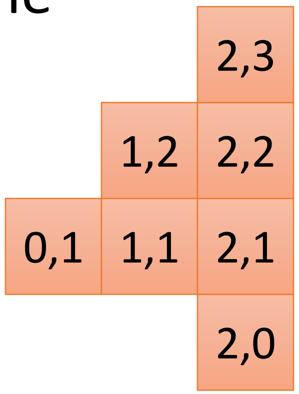

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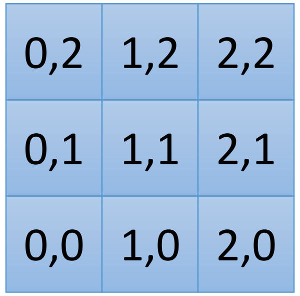

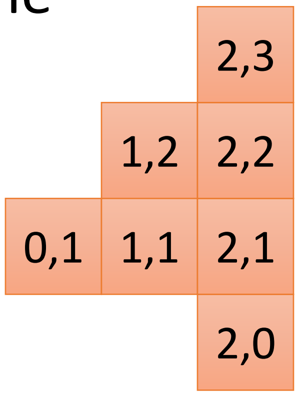

Complexity of self-assembled shapes

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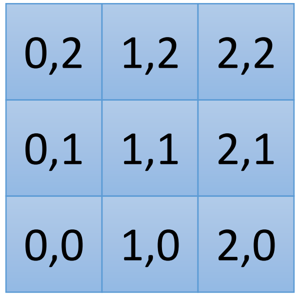

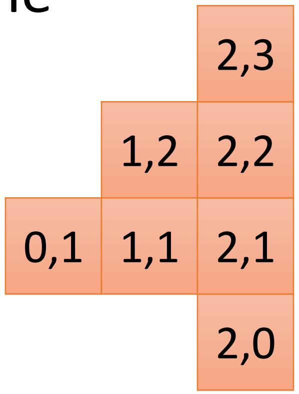

- Is there an infinite family of shapes $S_1, S_2, \ldots$, with $|S_n| = n$, such that each S_n requires <u>at least</u> n tile types to self-assemble?

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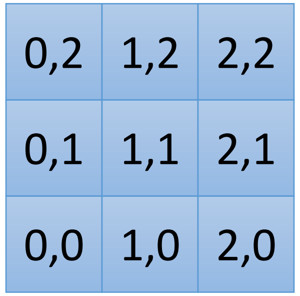

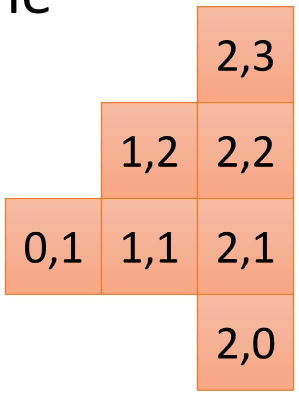

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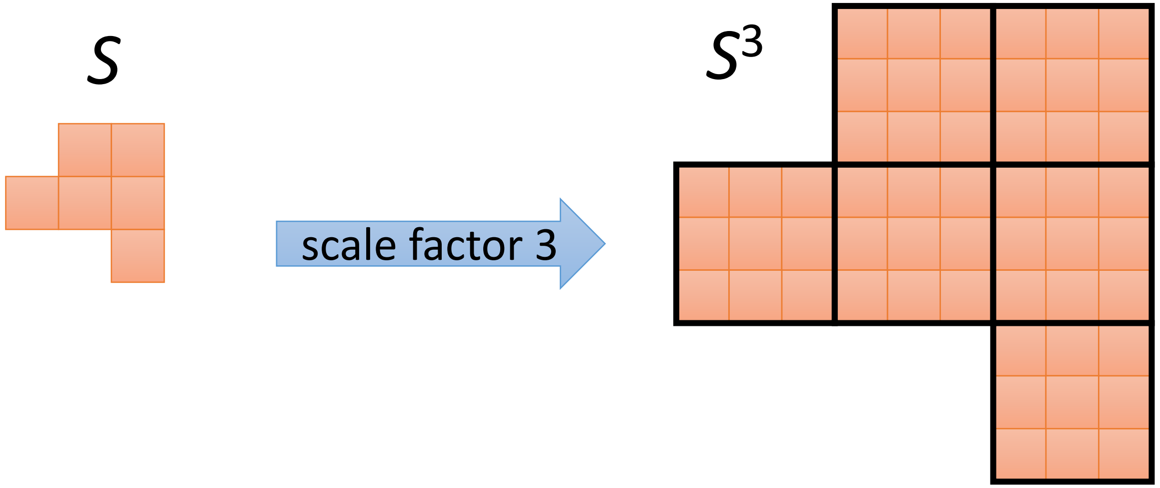
Complexity of self-assembled shapes

Suppose we are content to create a scaled up version of the shape:



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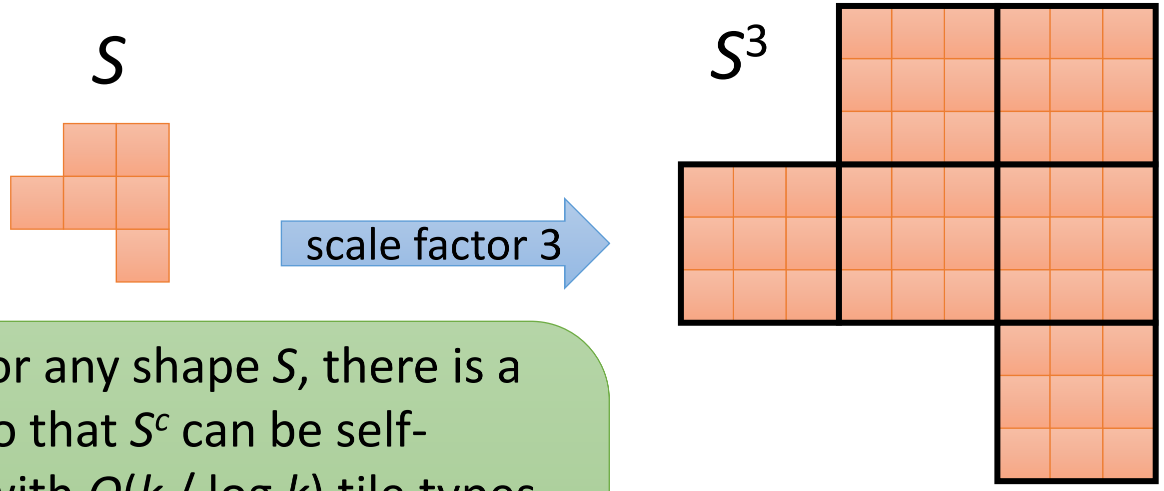

Theorem: For any shape S, there is a constant c so that S^c can be self-assembled with $O(k / \log k)$ tile types, where k is the length in bits of the shortest program (input to a universal Turing machine) that, on input (x,y), indicates whether $(x,y) \in S$.

[*Complexity of Self-Assembled Shapes*. Soloveichik and Winfree, SIAM Journal on Computing 2007]

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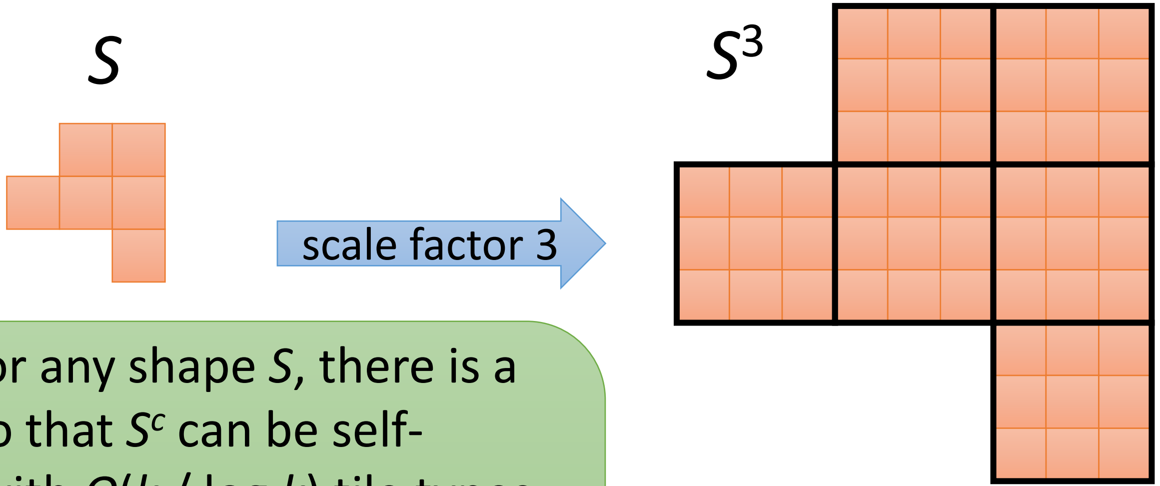

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Theorem (that we won't prove): This is optimal! No smaller tile system could self-assemble <u>any</u> scaling of S. If one existed, we could turn it into a program with $< k$ bits "describing" S in this way. (*Why?*)

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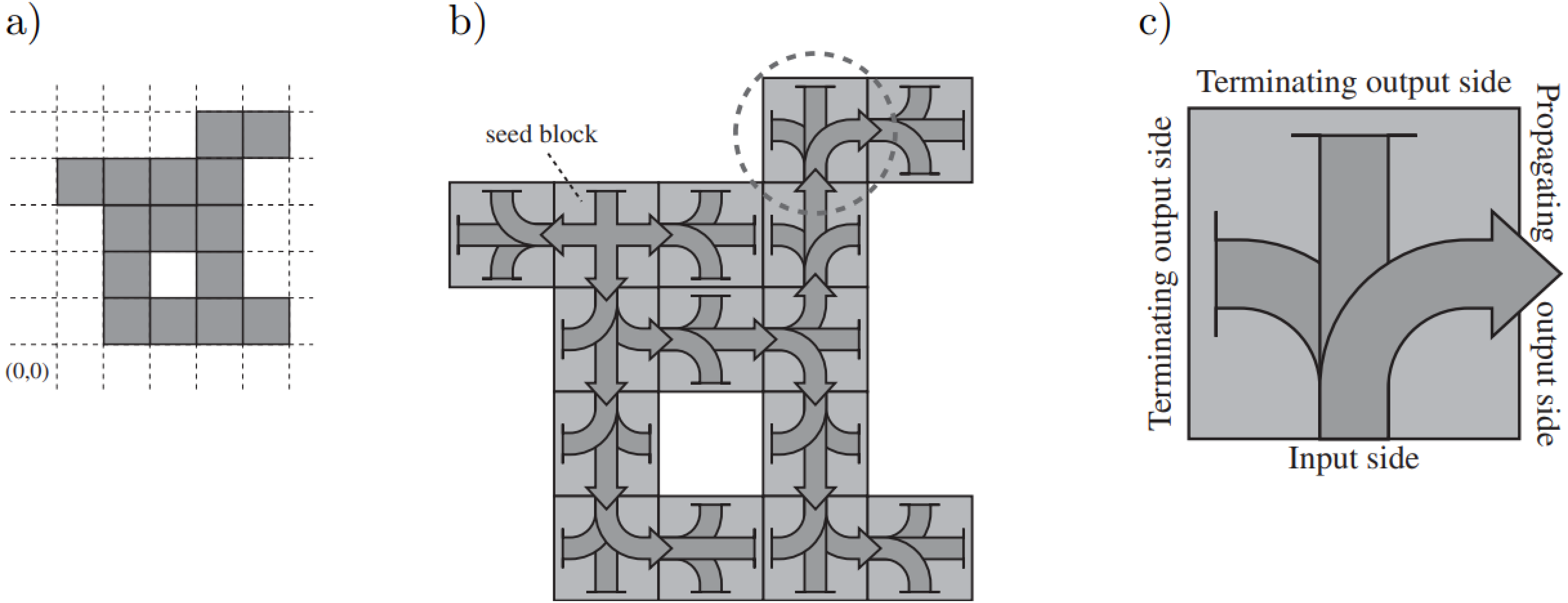

FIG. 5.1. *Forming a shape out of blocks:* (a) *A coordinated shape S.* (b) *An assembly composed of $c \times c$ blocks that grow according to transmitted instructions such that the shape of the final assembly is $\tilde{S}$ (not drawn to scale). Arrows indicate information flow and order of assembly. The seed block and the circled growth block are schematically expanded in Figure 5.2.* (c) *The nomenclature describing the types of block sides.*

Programming a shape (inaccurate cartoonish overview)

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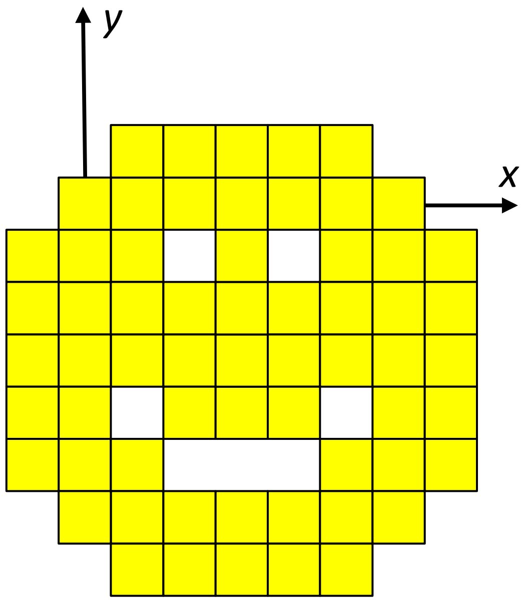

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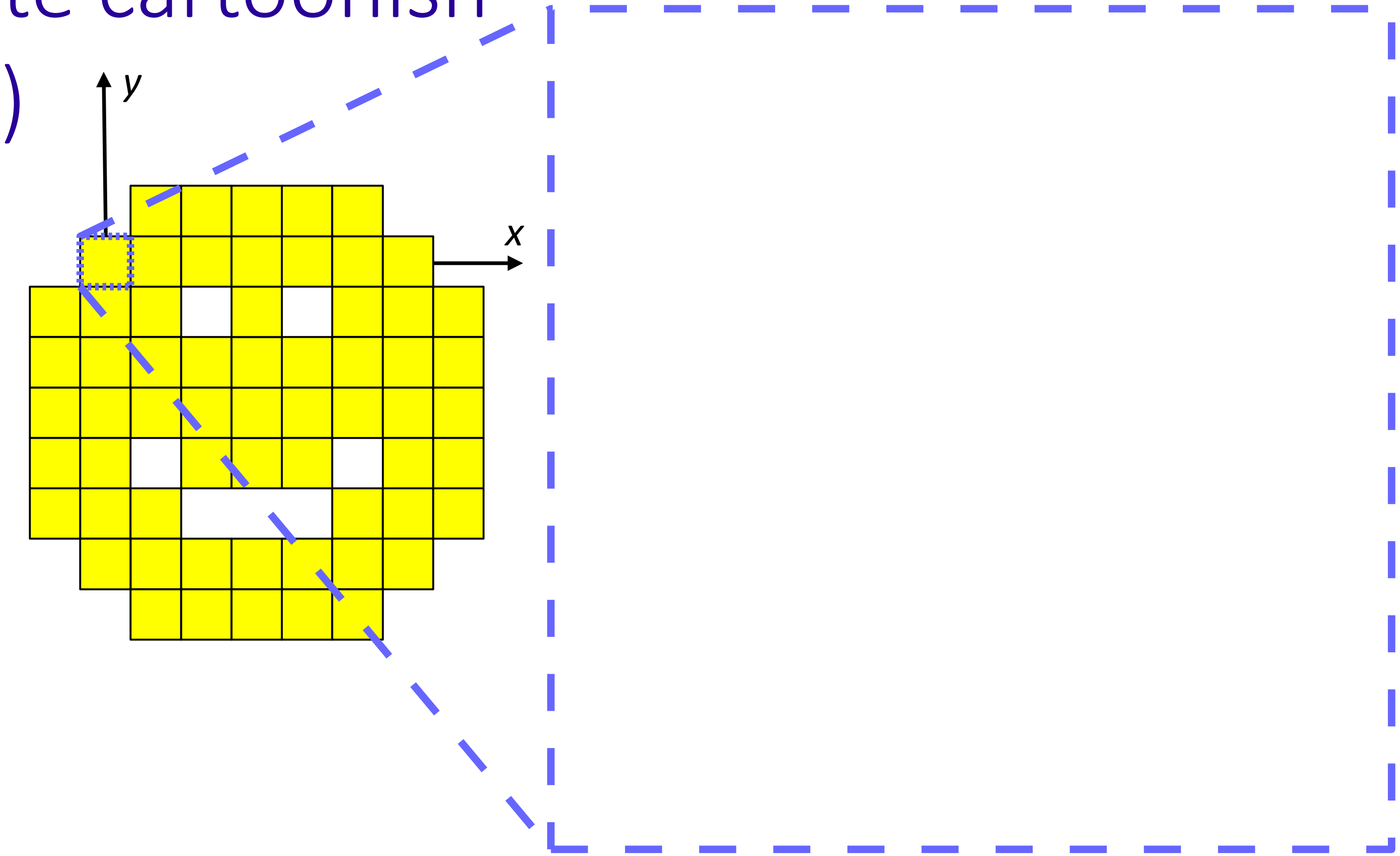

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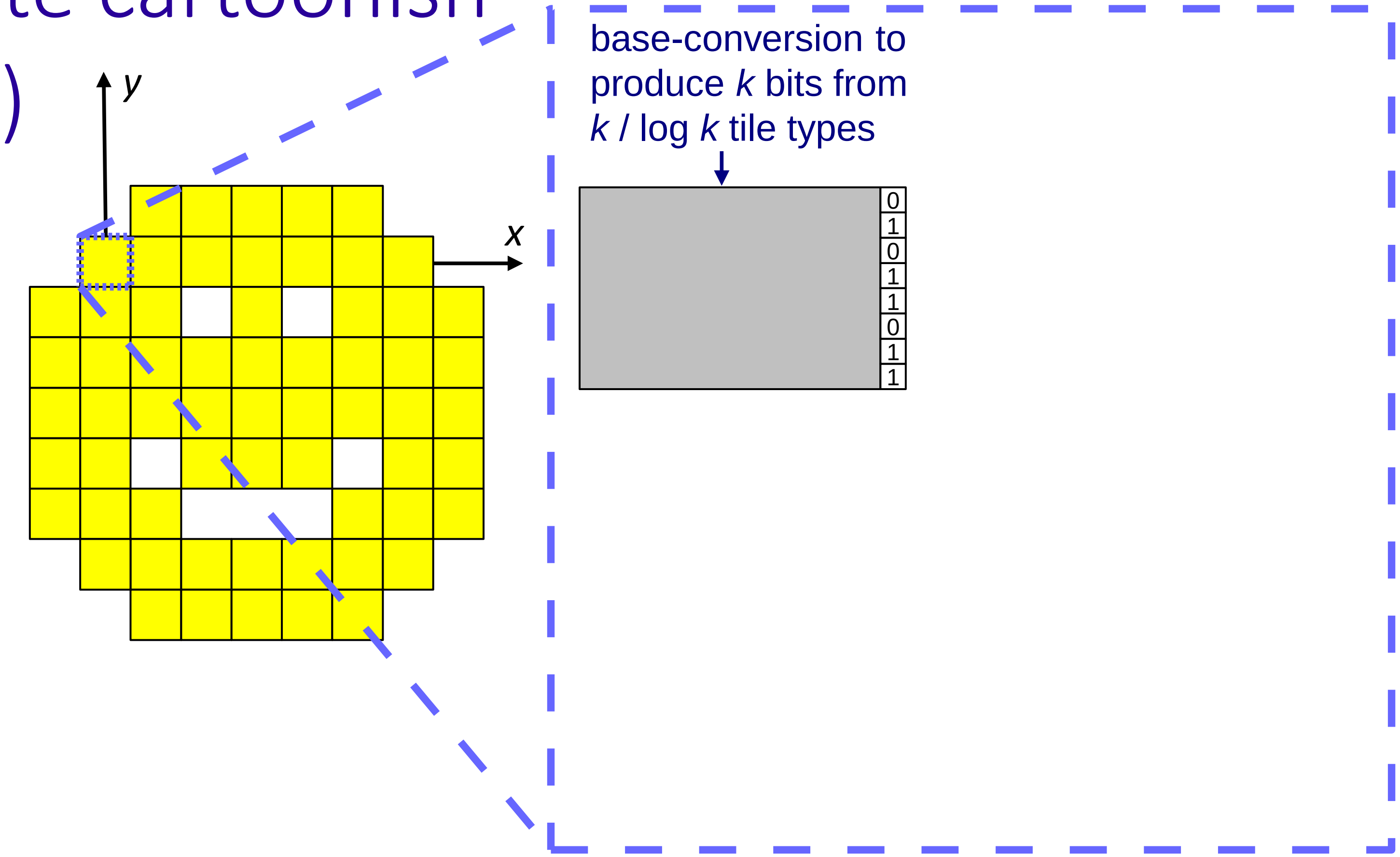

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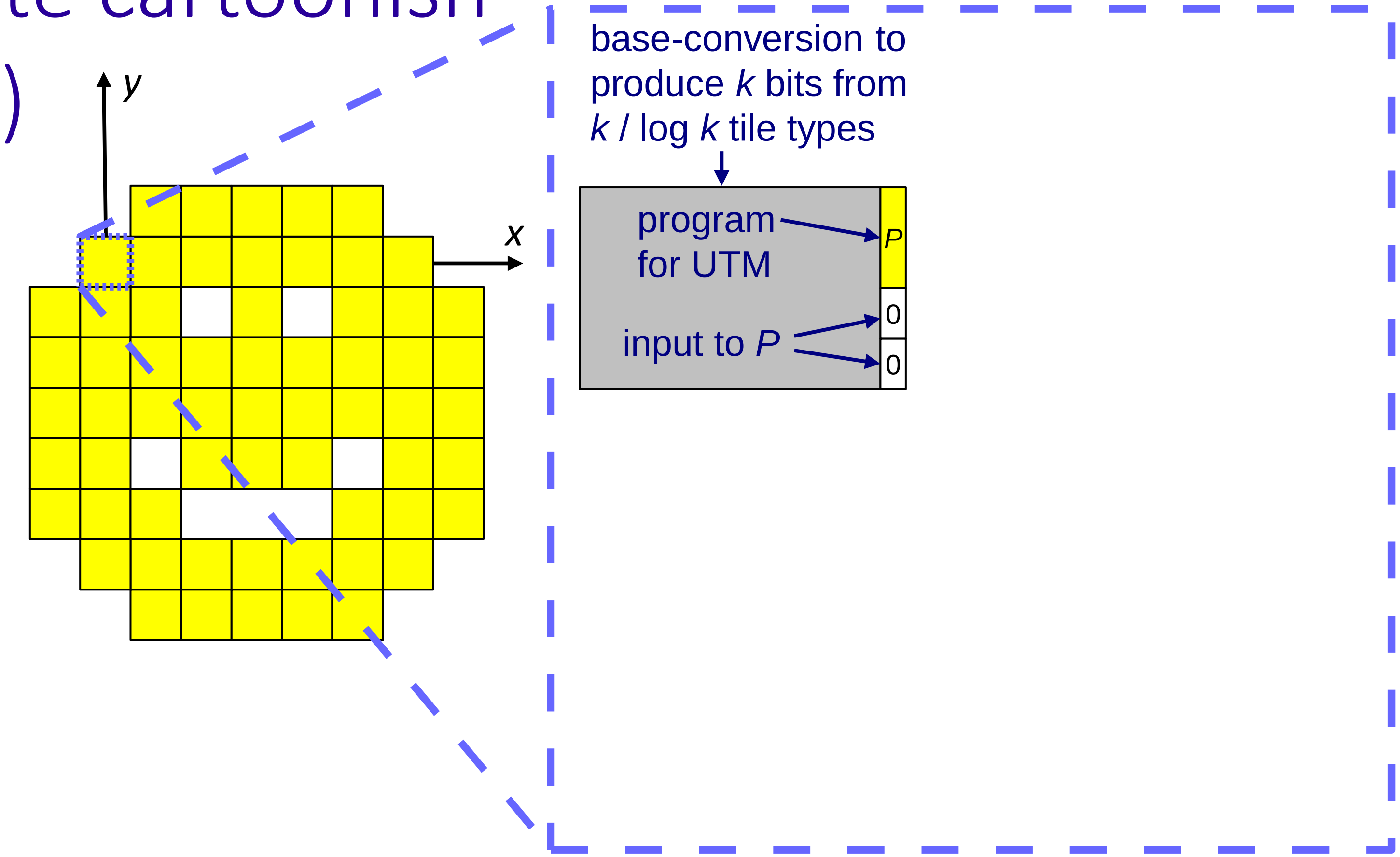

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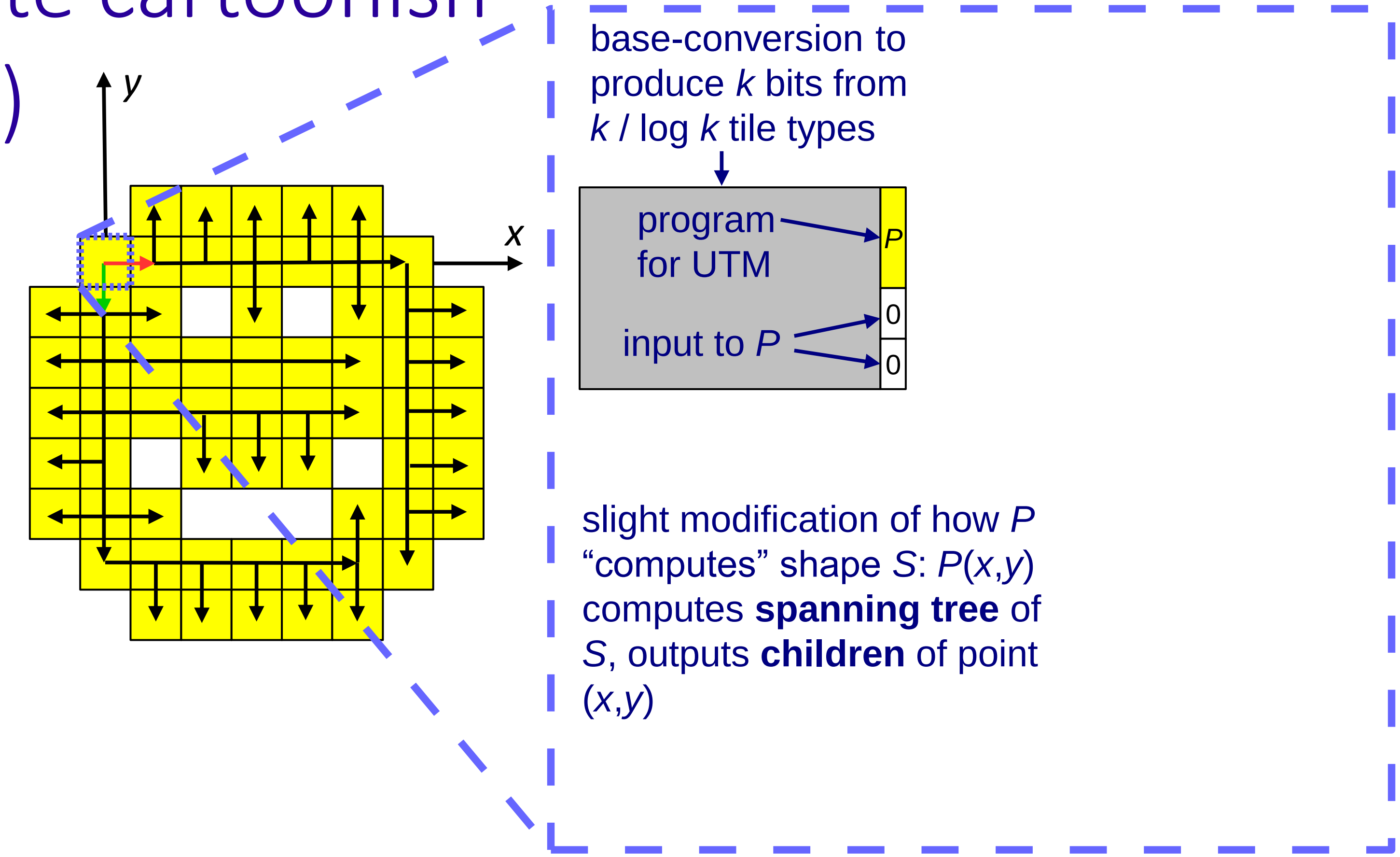

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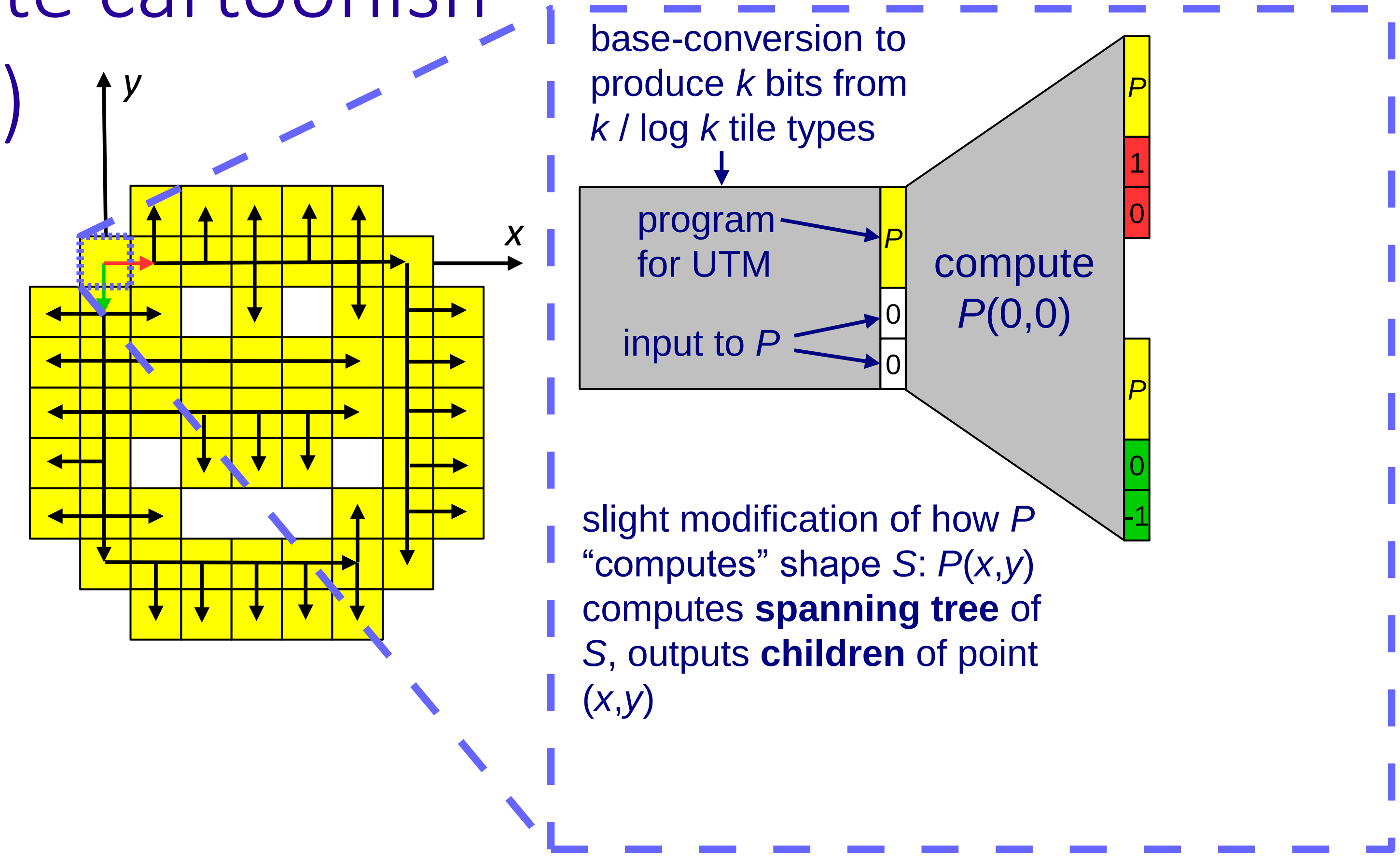

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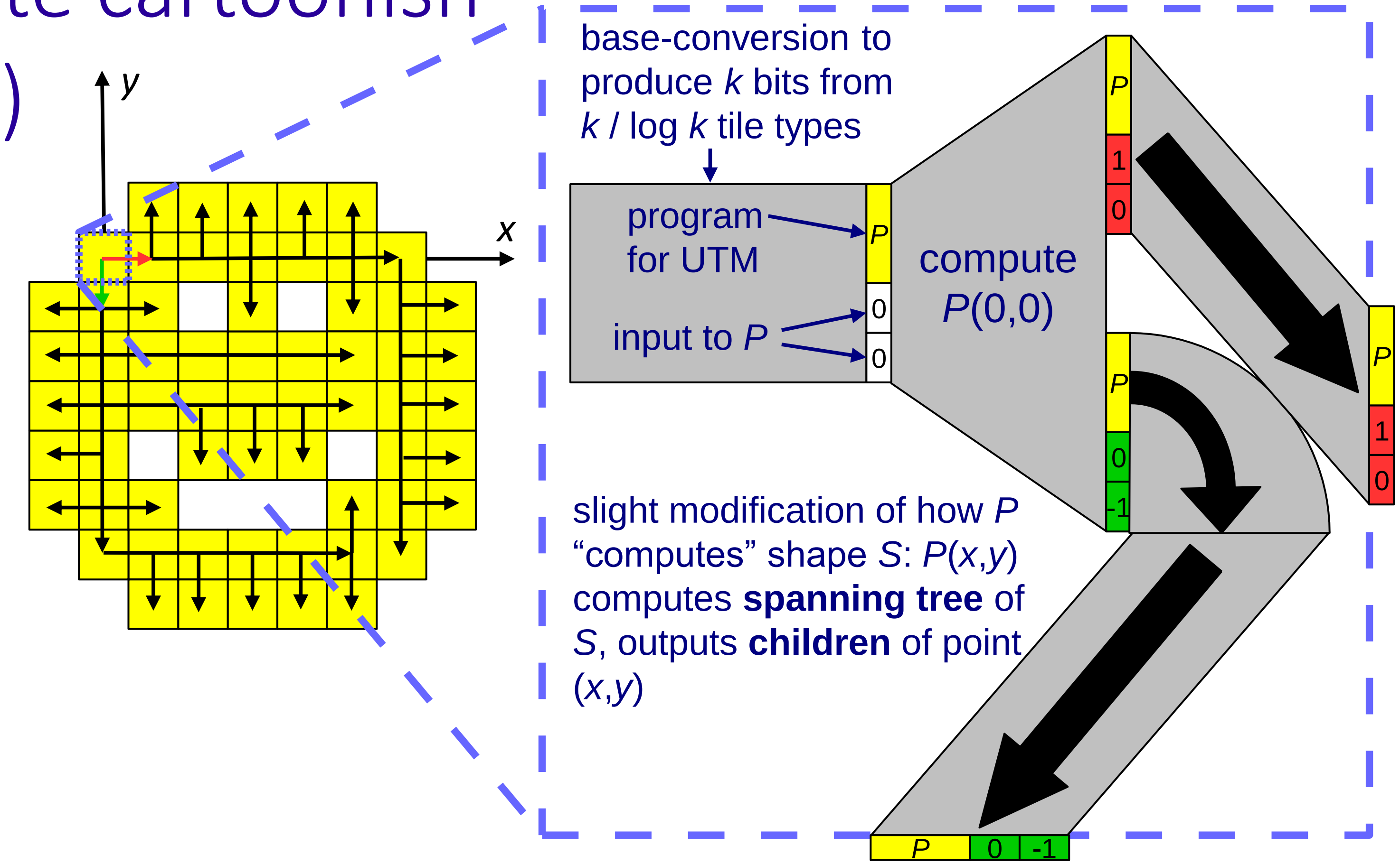

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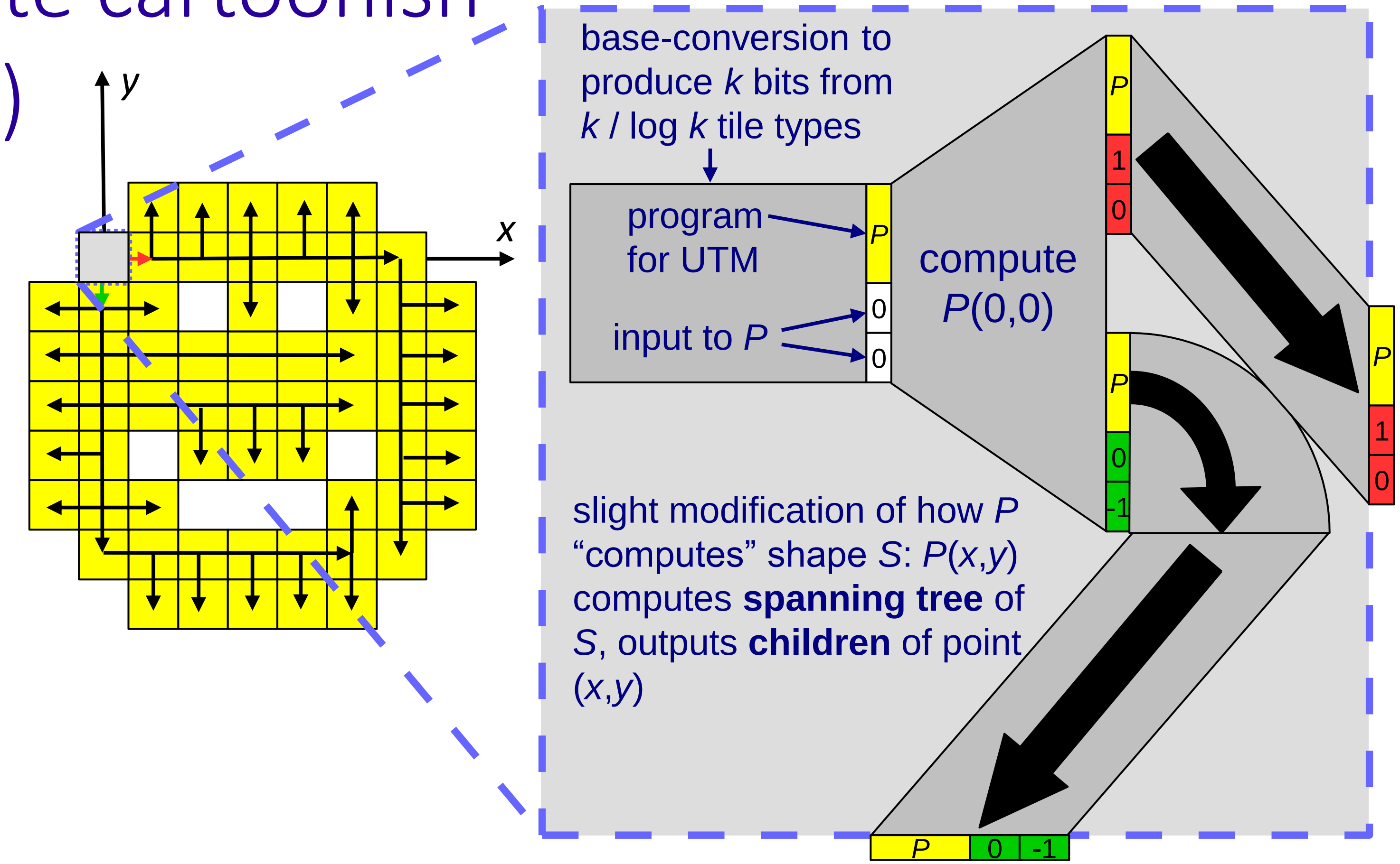

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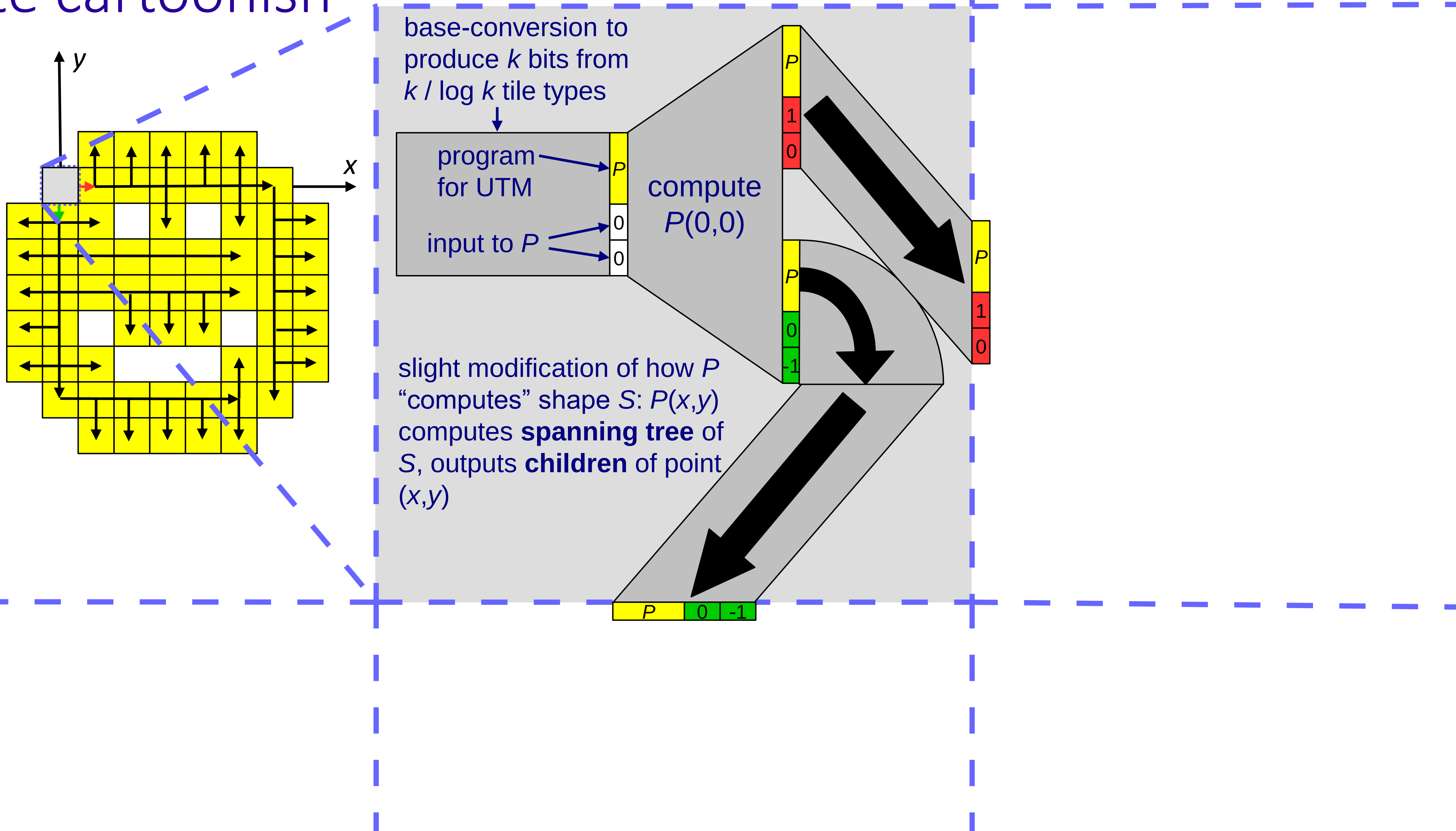

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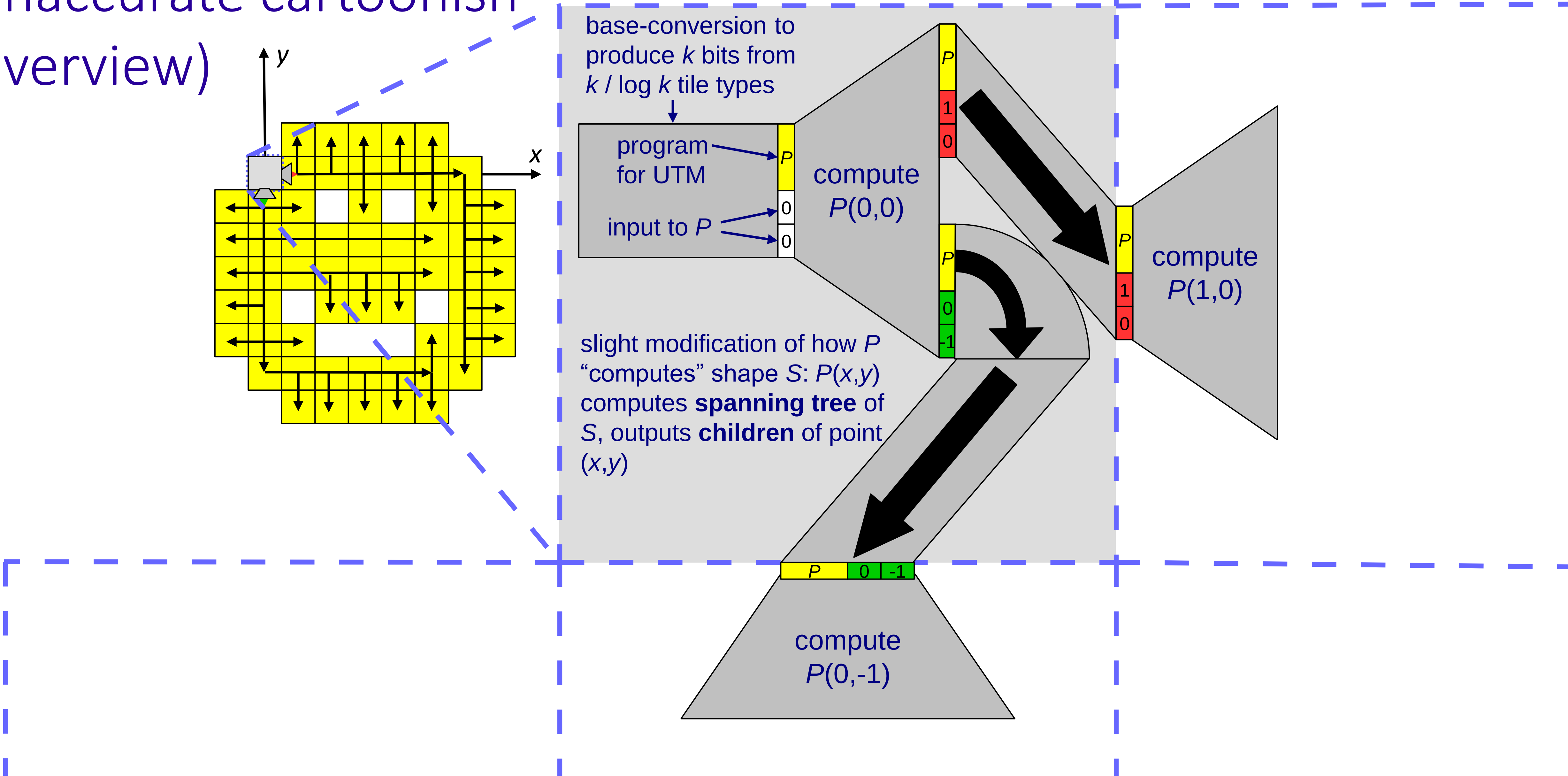

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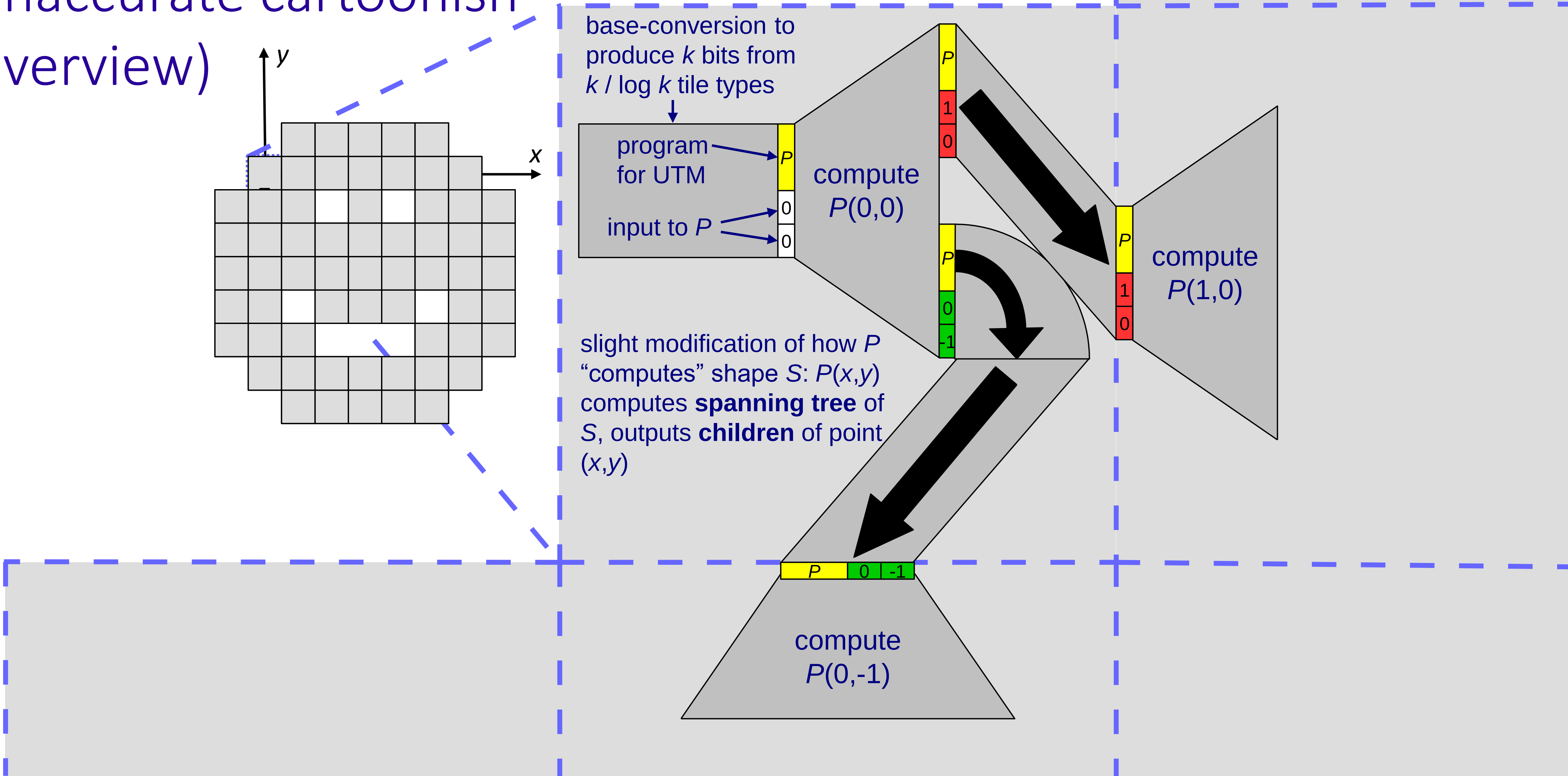
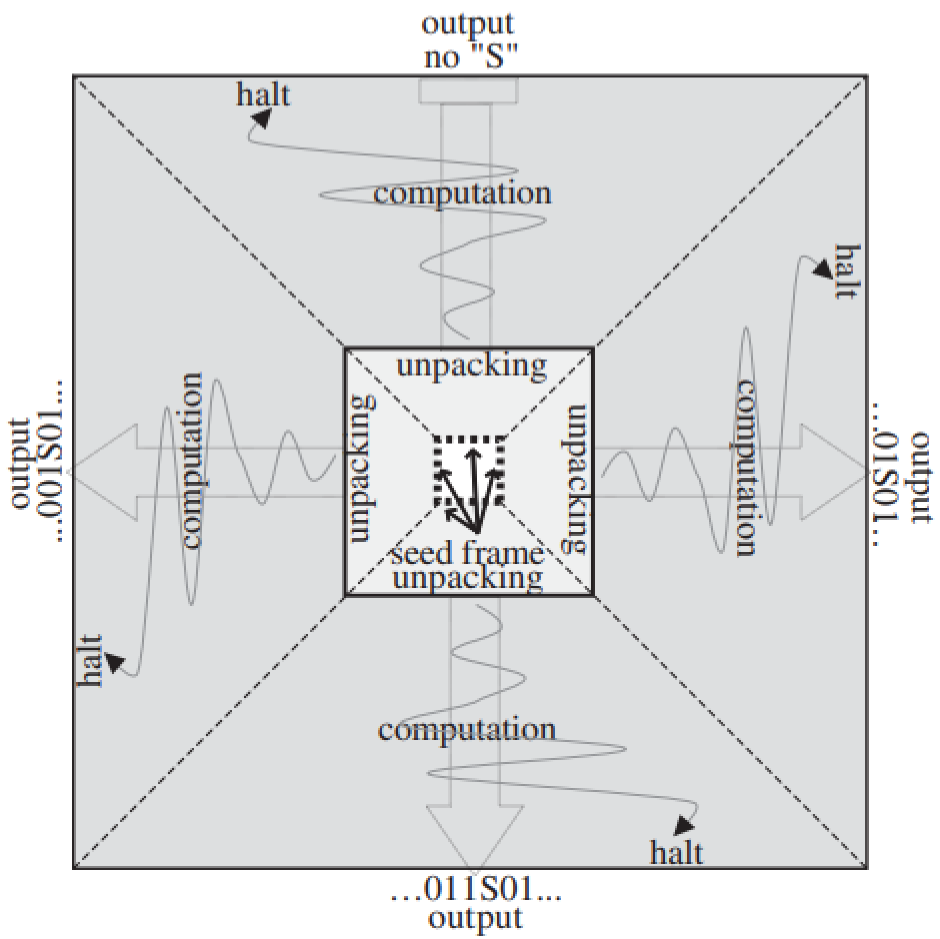
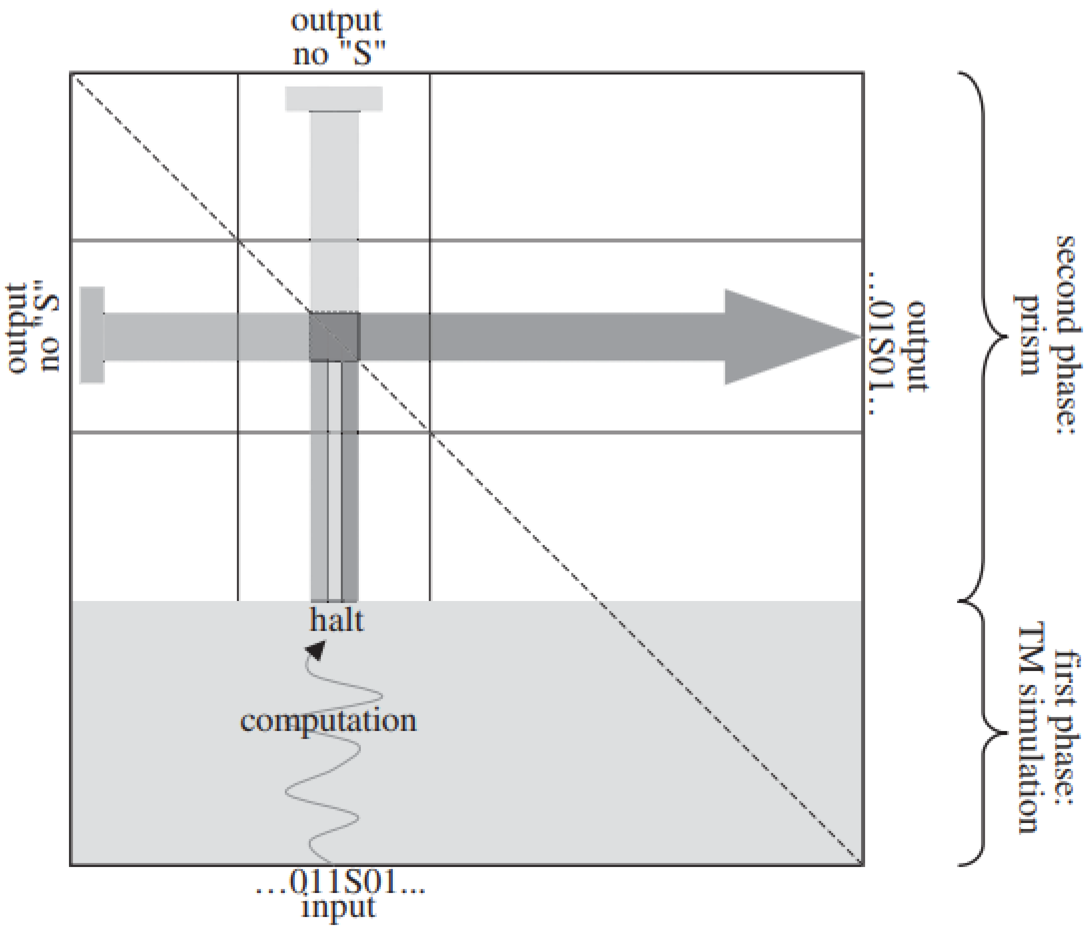


More accurate detailed overview

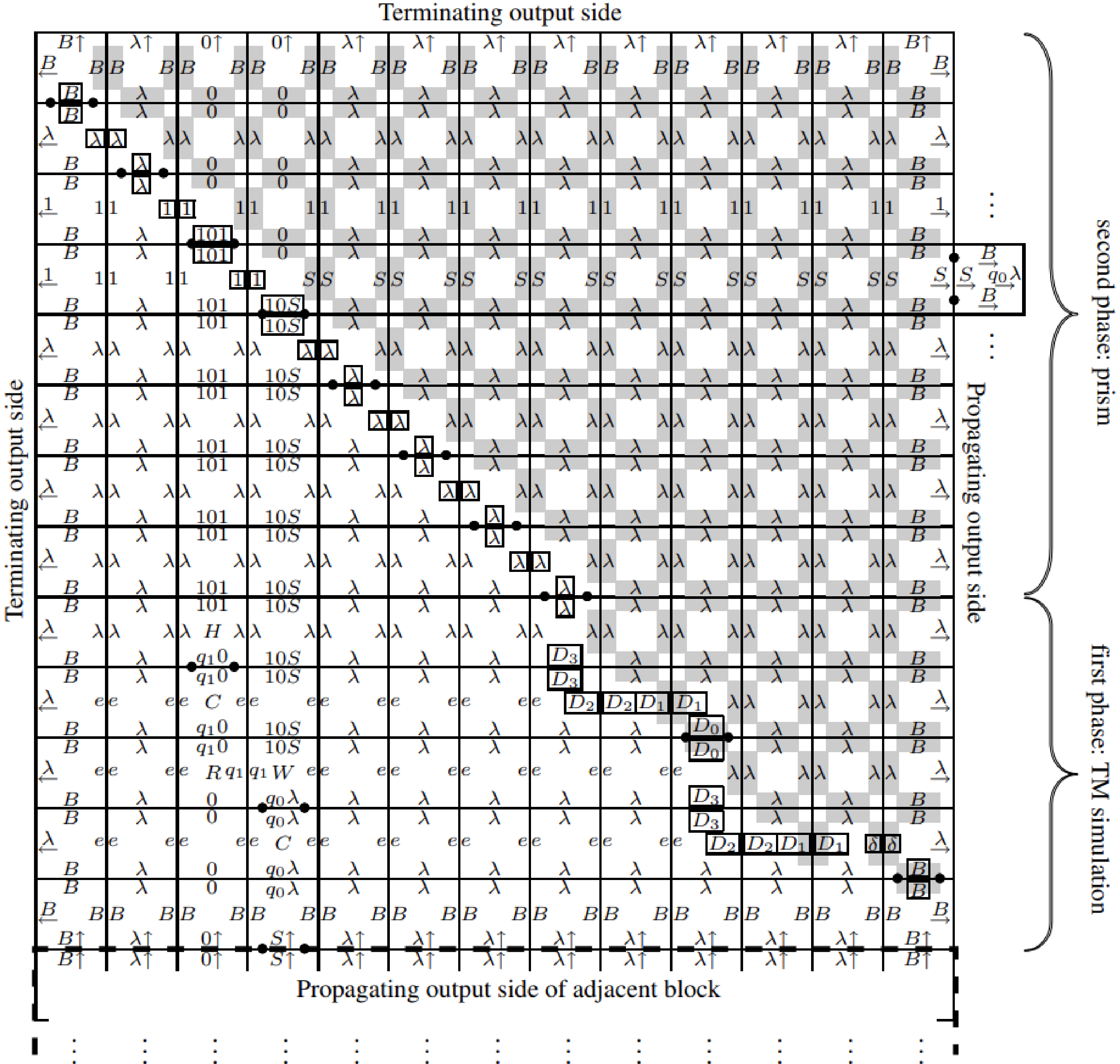
seed block



growth block



fully-detailed example of growth block



Two interpretations

as stated for single seed tile:

Theorem: For any shape S, there is a constant c so that S^c can be self-assembled with $O(k / \log k)$ tile types, where k is the length in bits of the shortest program (input to a universal Turing machine) that, on input (x,y), indicates whether $(x,y) \in S$.

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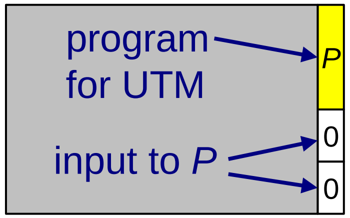
$\sigma_S =$ 

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i.e., T is a **universal** set of tile types that can self-assemble any shape, by giving it the right seed.

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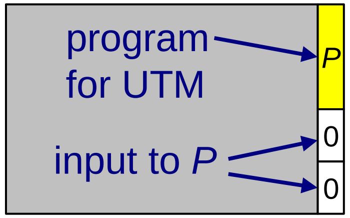
$\sigma_S =$ 

Strict and weak self-assembly

Computability-theoretic questions about self-assembly

Strict and weak self-assembly

Recall:

Let $X \subseteq \mathbb{Z}^2$ be a **shape**, a connected subset of $\mathbb{Z}^2$. Θ **strictly self-assembles** X if, for all $\alpha \in A_{\square}[\Theta]$, $S_\alpha = X$.
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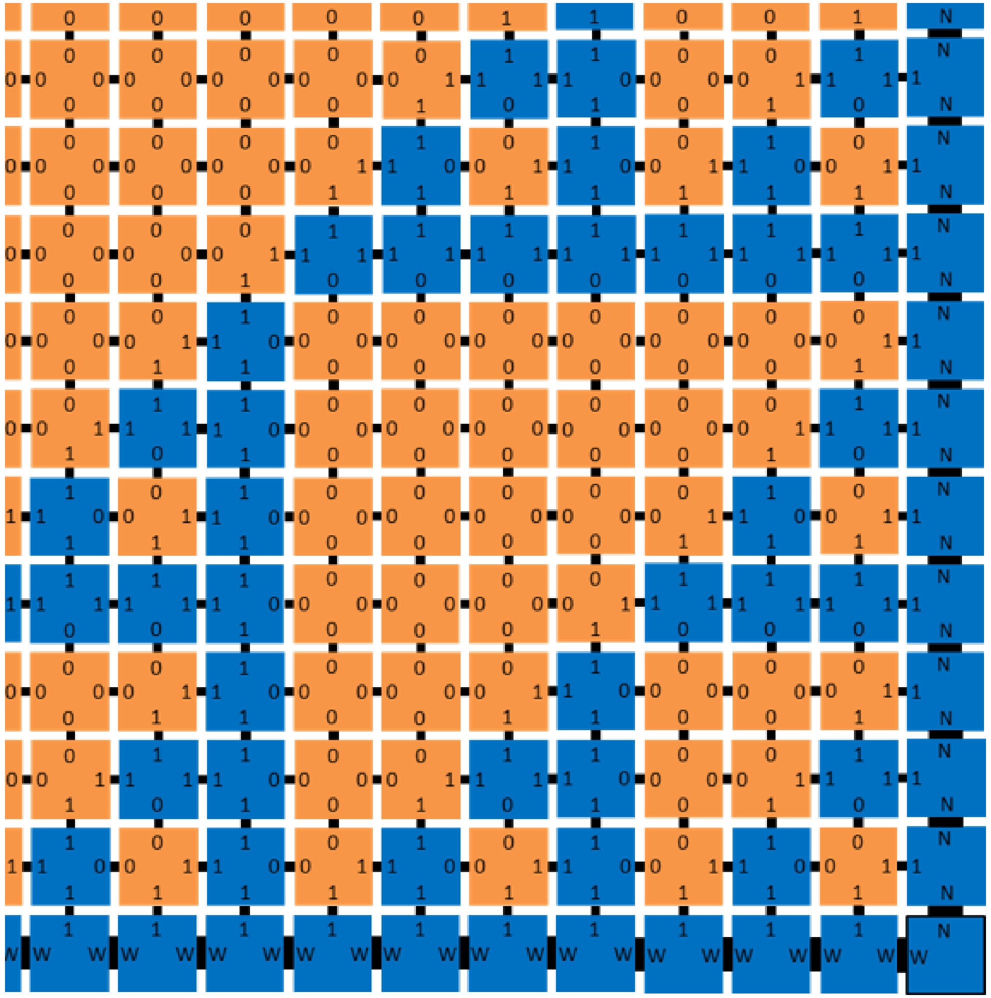
Tile system on right strictly self-assembles the whole second quadrant, and it weakly self-assembles the discrete Sierpinski triangle.



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Use that fact now to define an explicit shape that cannot be strictly self-assembled.

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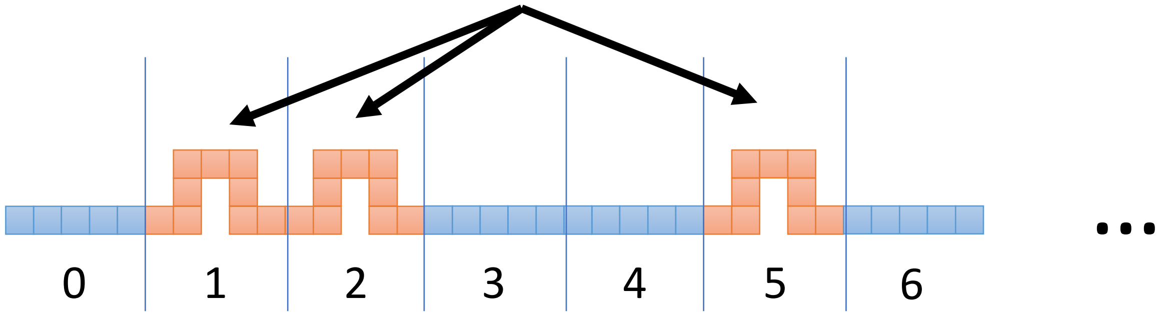

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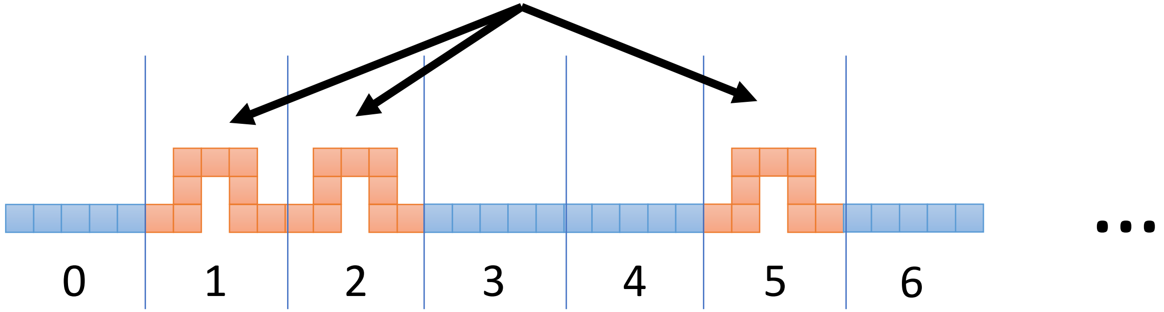
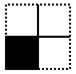


Question: Is there a computable shape $S \subseteq \mathbb{Z}^2$ that cannot be strictly self-assembled?

A famous fractal

- Let S_0 = { (0,0) }
- Let V = { (0,0), (0,1), (1,0) } be three vectors for “recursive translation”.



S_0

[slide credit:
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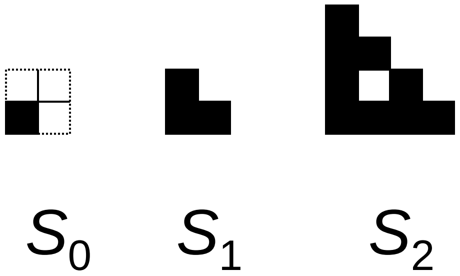

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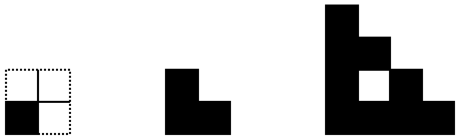

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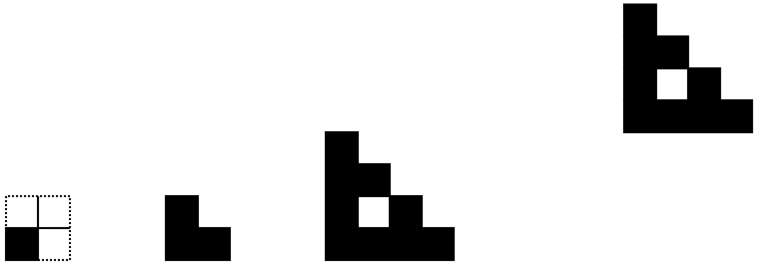

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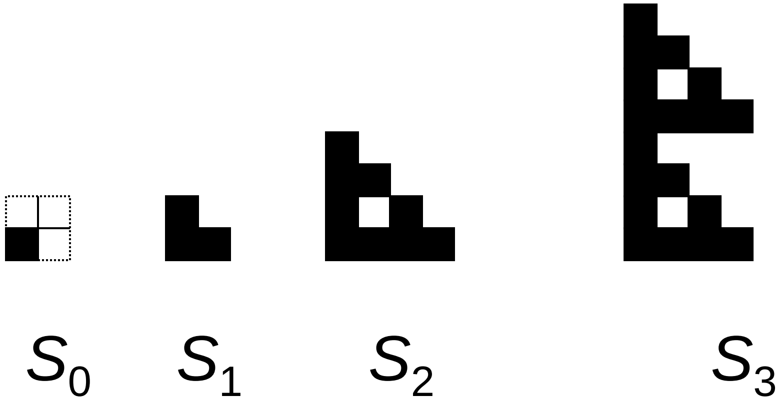

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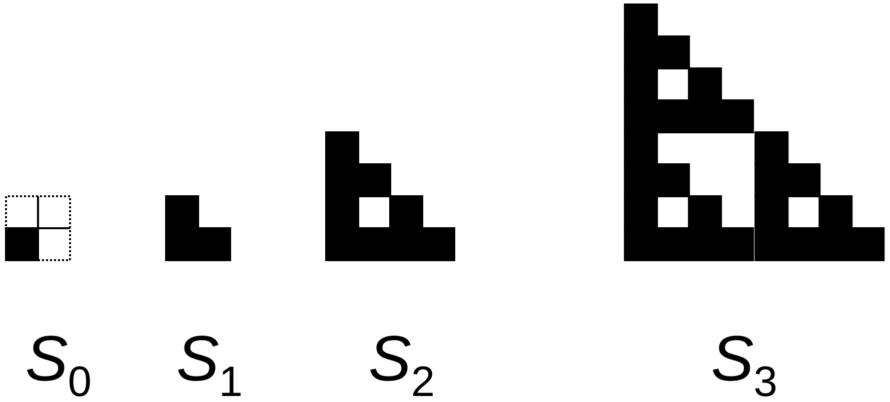

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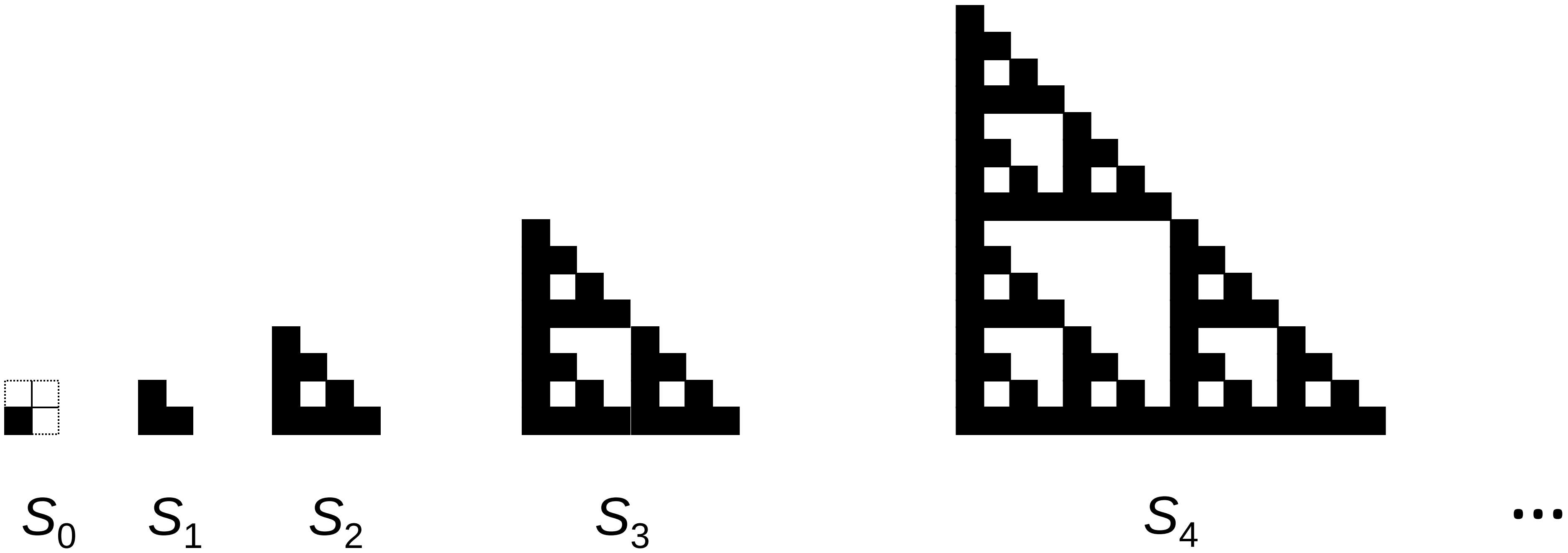

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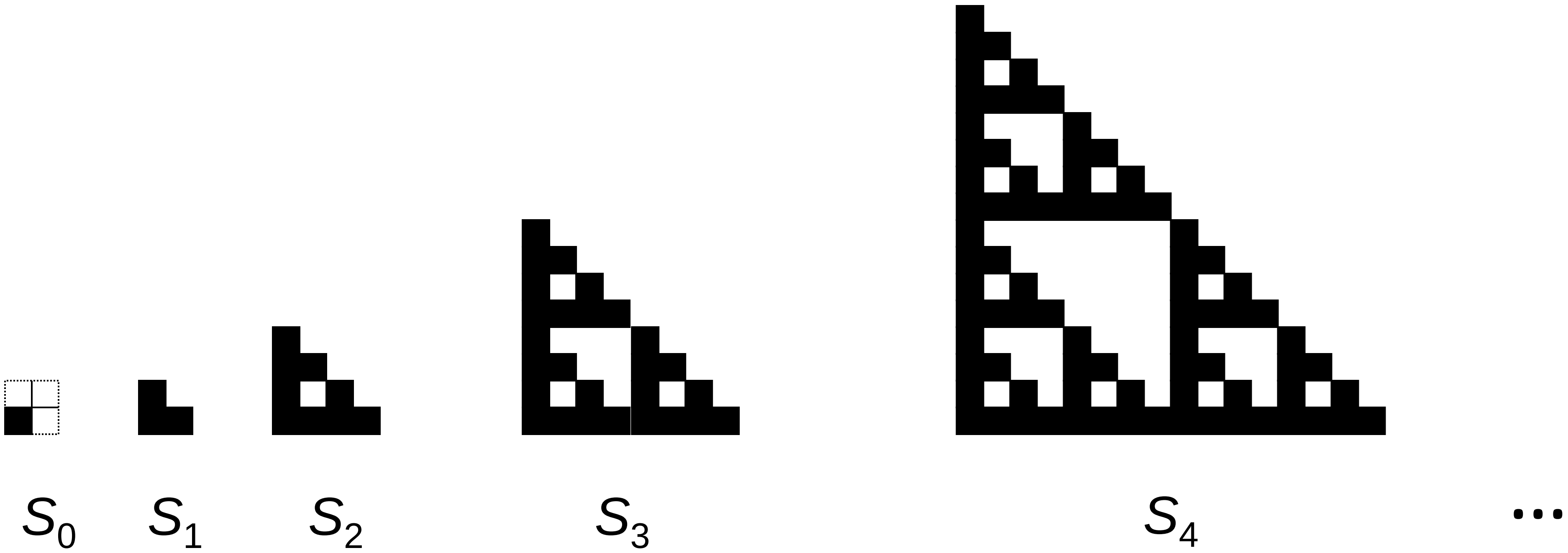

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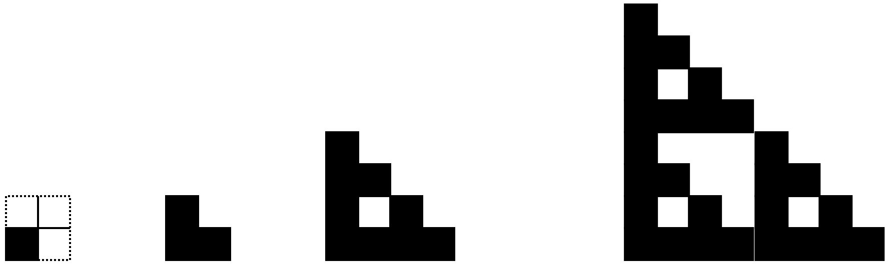
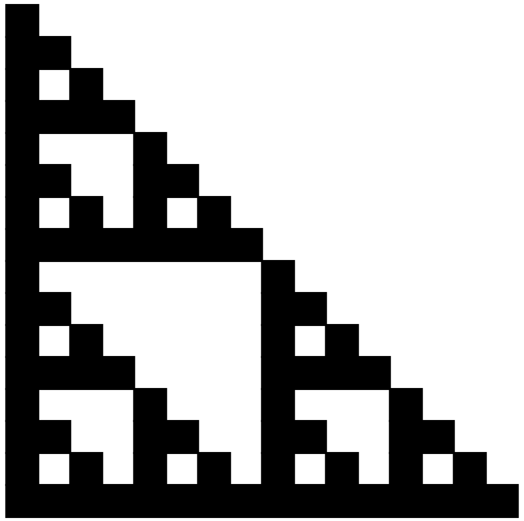
Observation: *S* is computable (easily).





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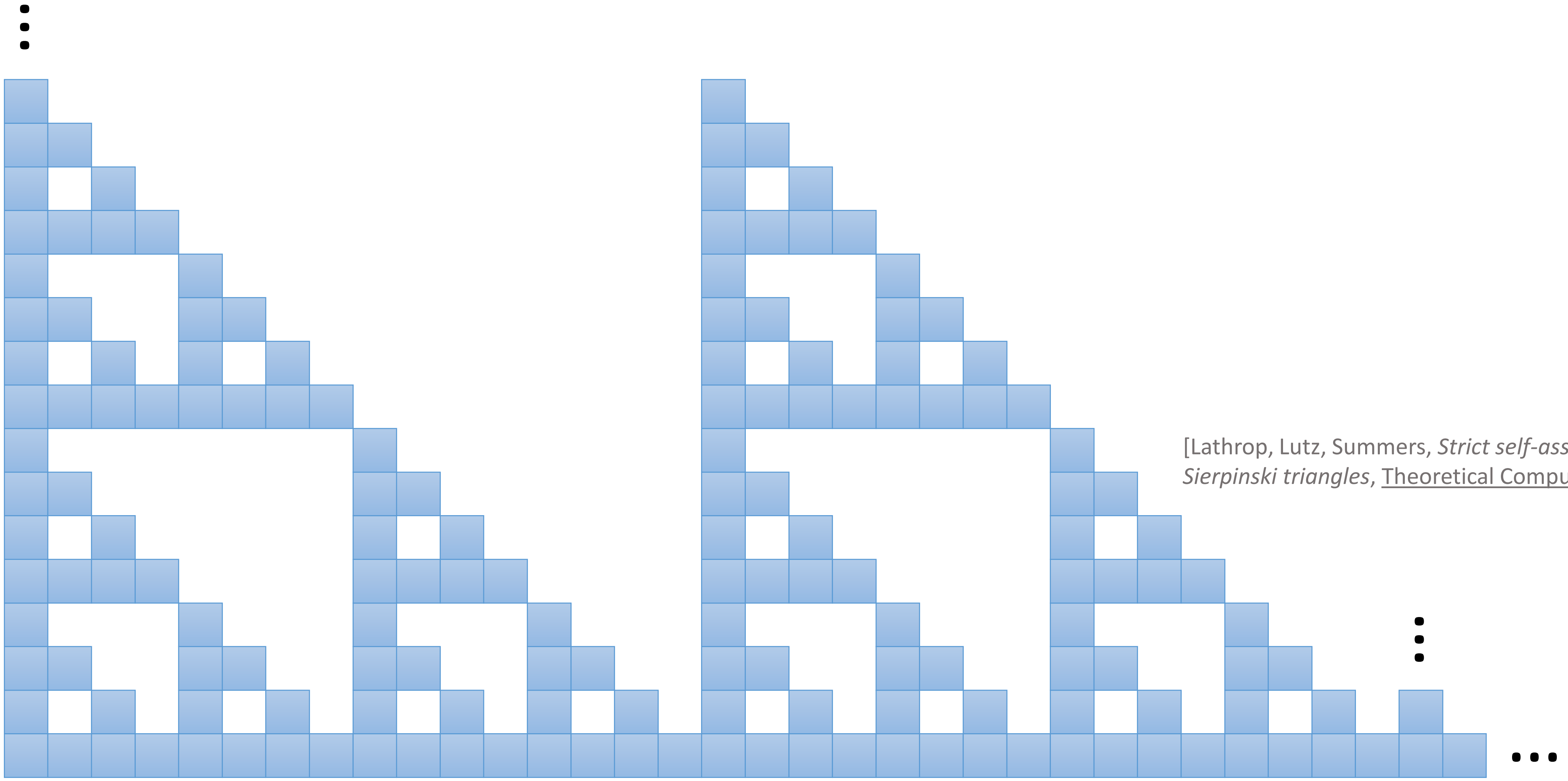
S_0 S_1 S_2 S_3 S_4 …

The discrete Sierpinkski triangle cannot be strictly self-assembled



[Lathrop, Lutz, Summers, *Strict self-assembly of discrete Sierpinski triangles*, Theoretical Computer Science 2009.]

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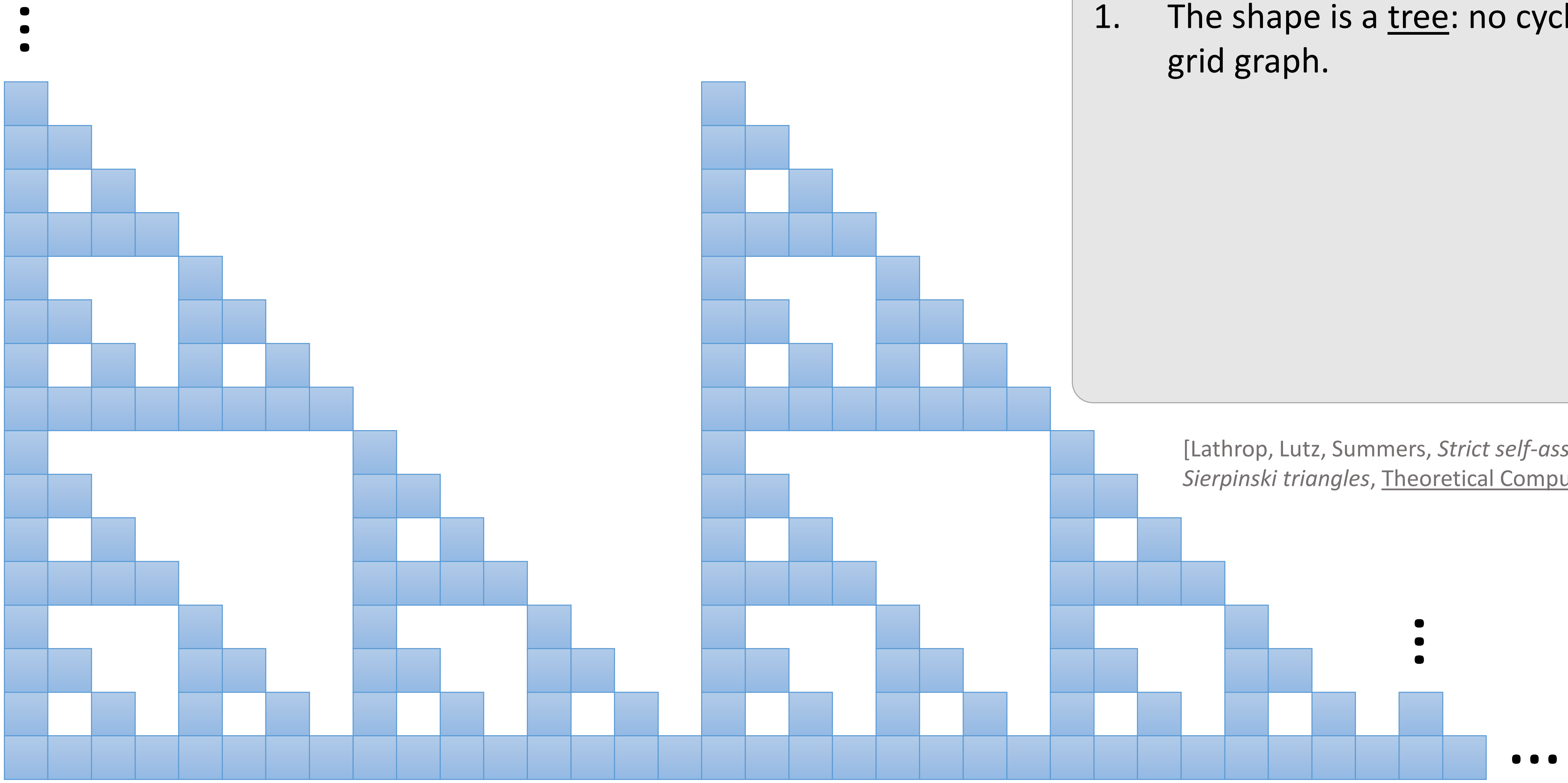

Proof:

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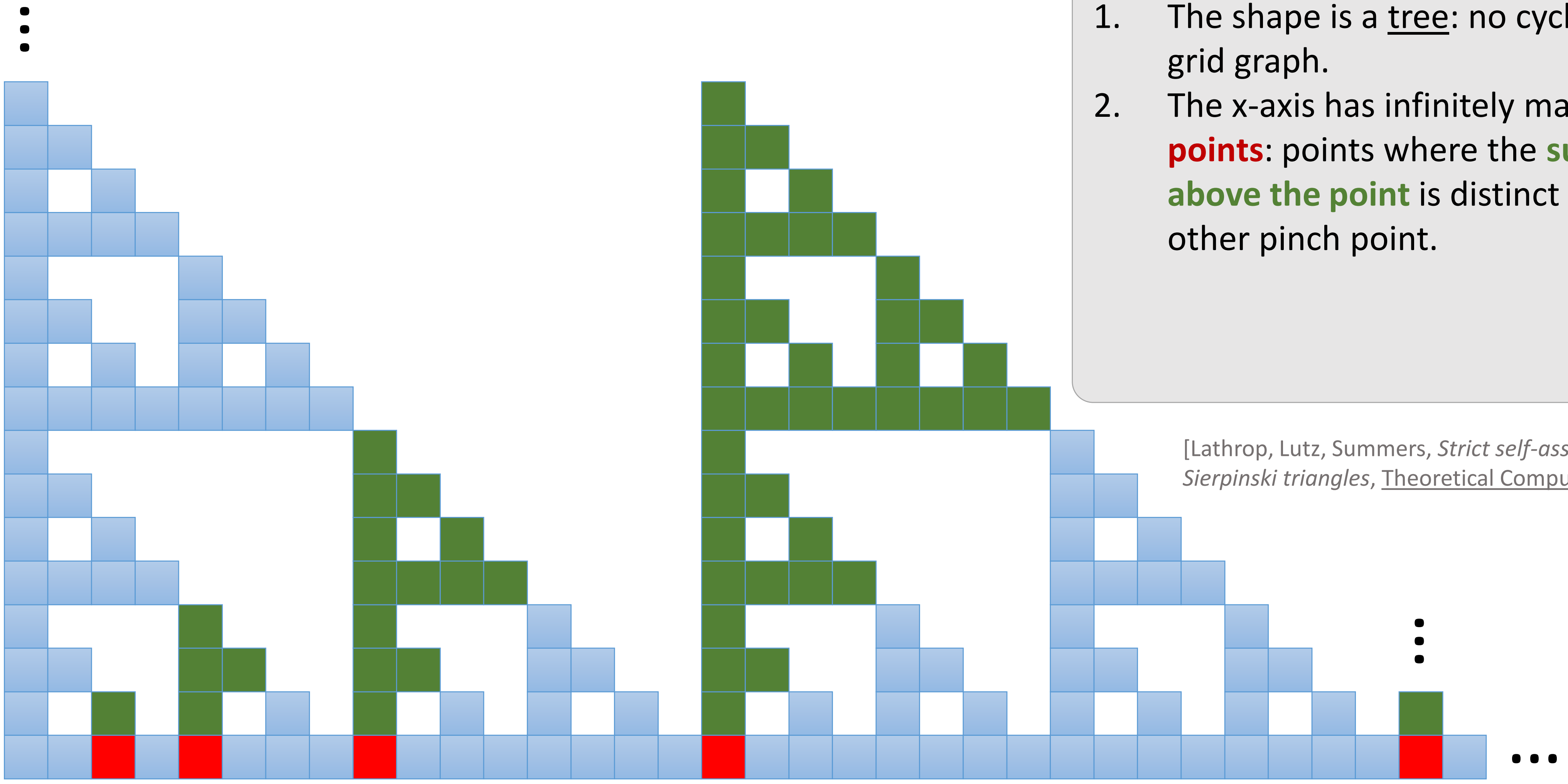

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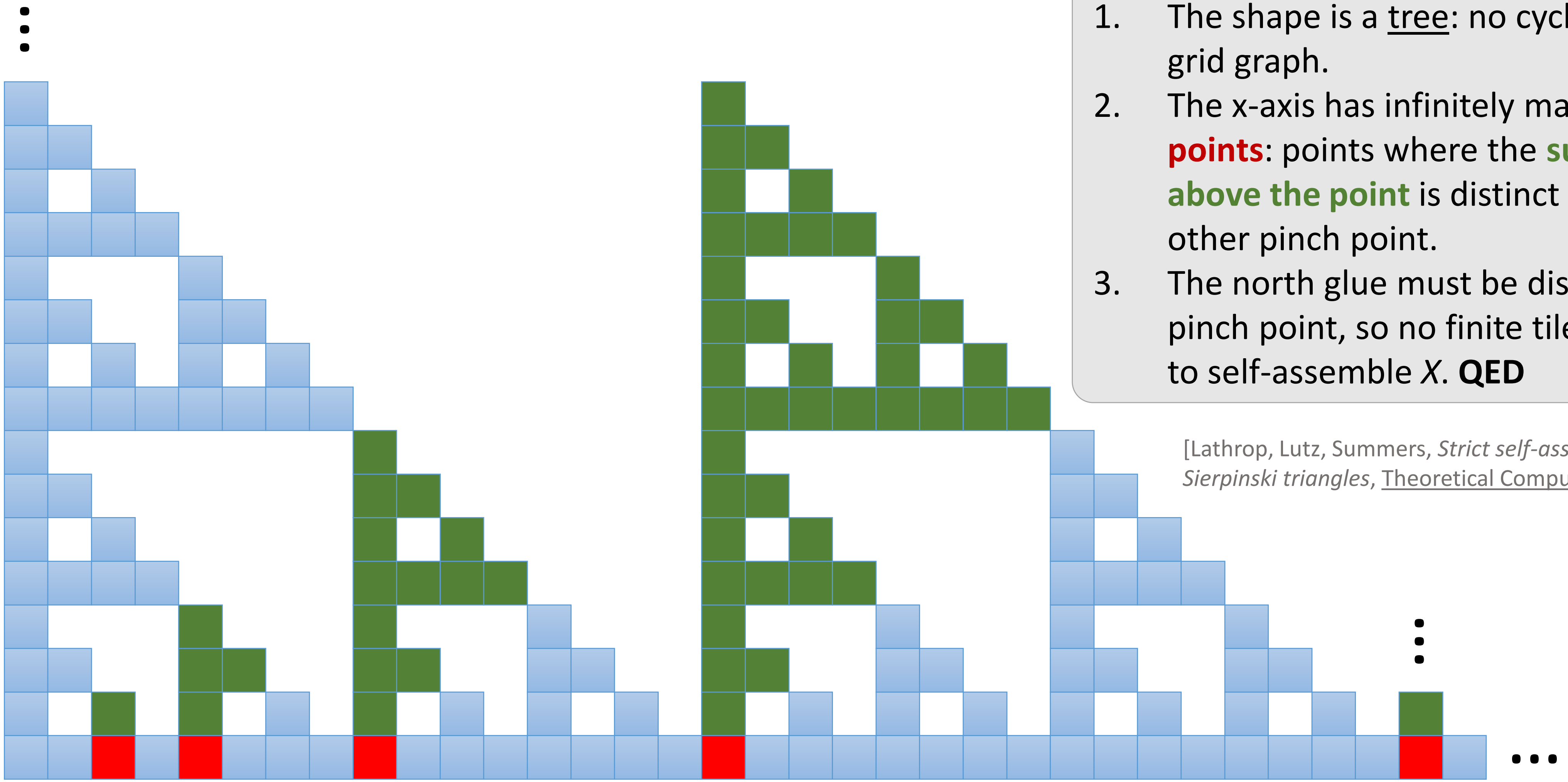

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3. The north glue must be distinct at each pinch point, so no finite tile set suffices to self-assemble *X*. **QED**

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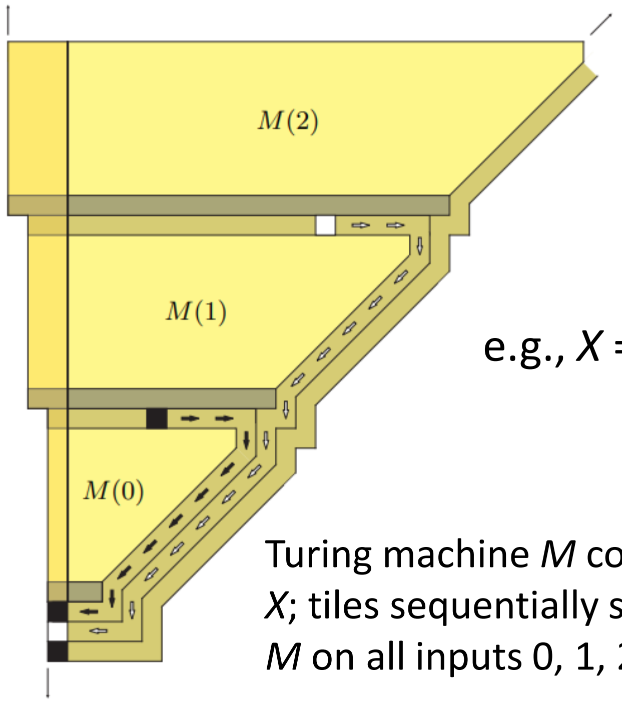
Weak self-assembly

Theorem: Every computable set $X \subseteq \mathbb{N}$, "embedded straightforwardly" in $\mathbb{Z}^2$, can be weakly self-assembled.



e.g., X = {0, 2, …}

Turing machine M computes X; tiles sequentially simulate M on all inputs 0, 1, 2, …,

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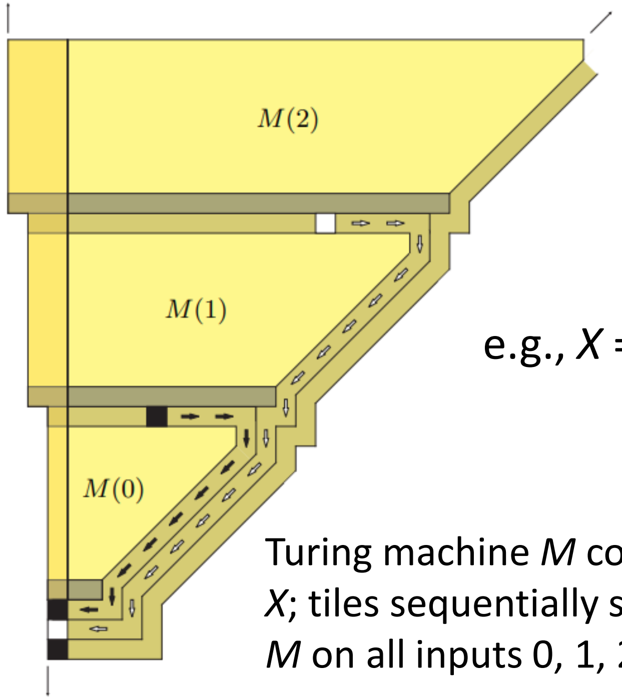

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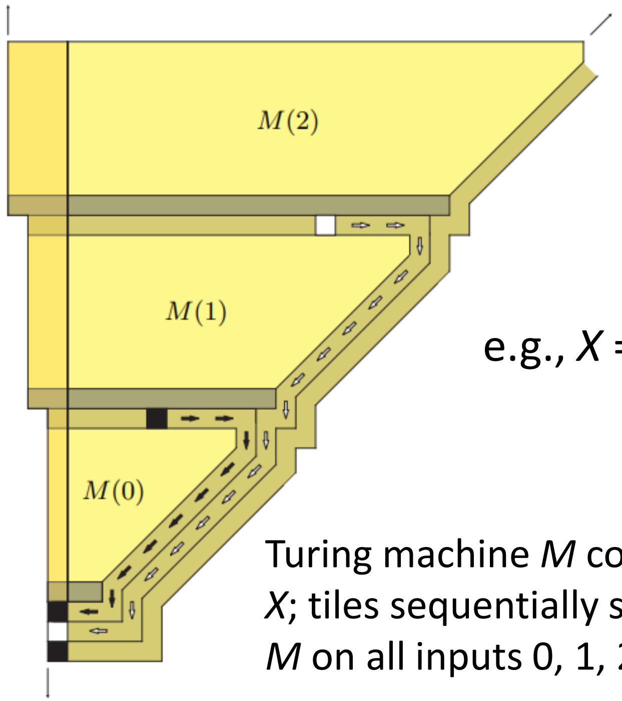

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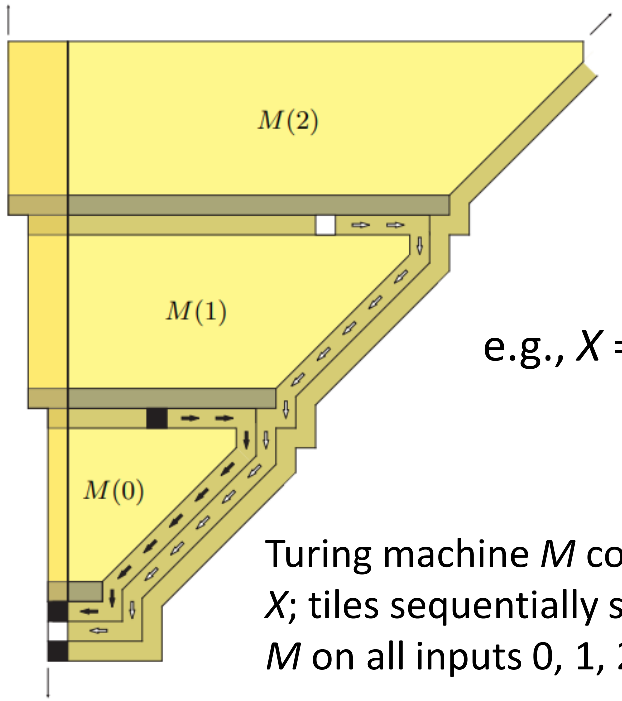

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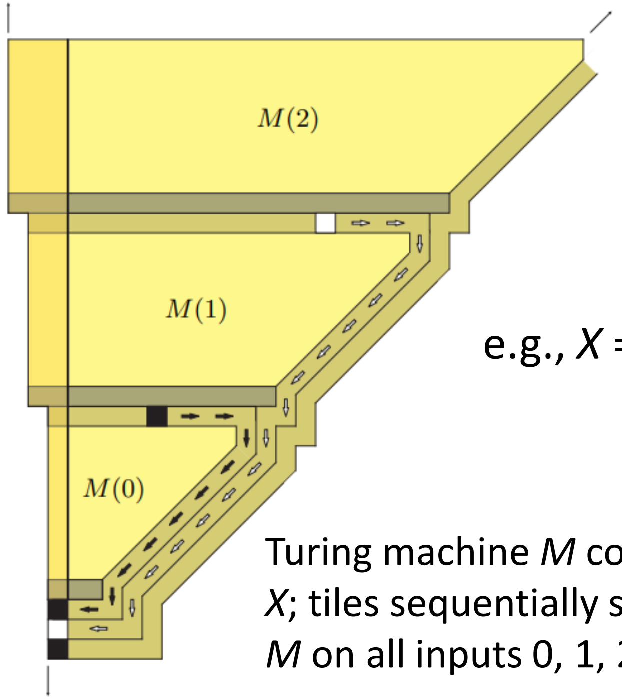

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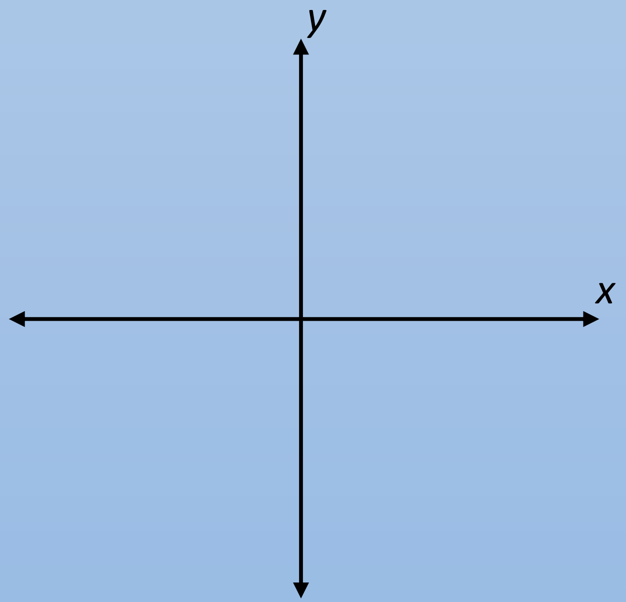

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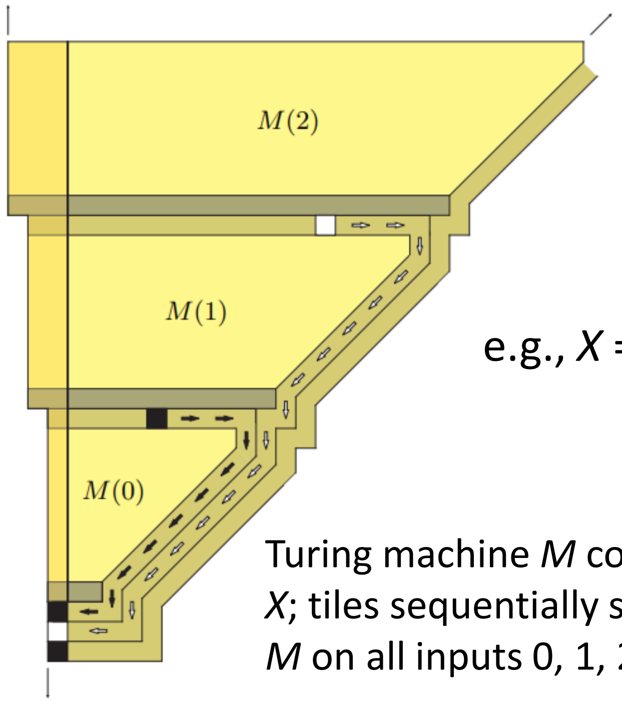

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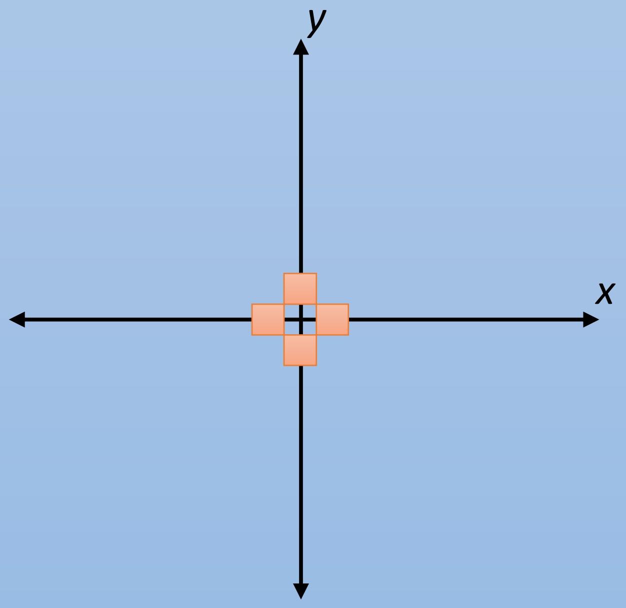

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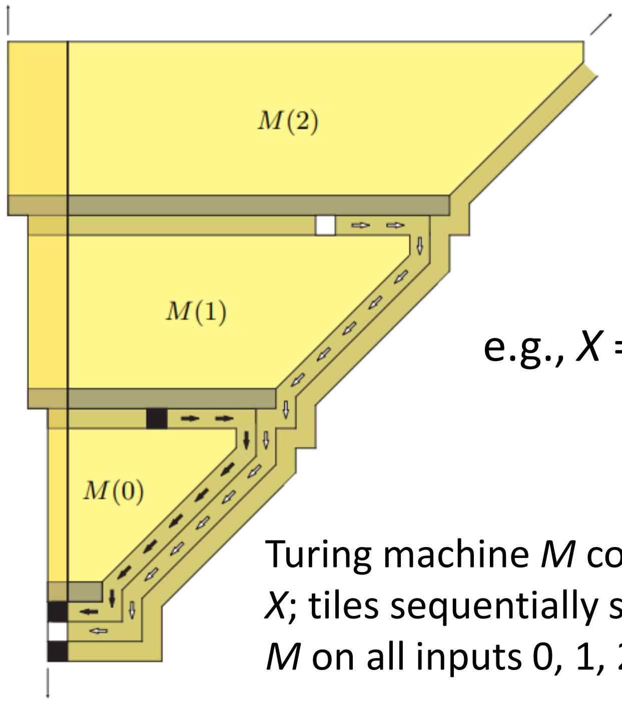

e.g., $X = \{0, 2, \ldots\}$

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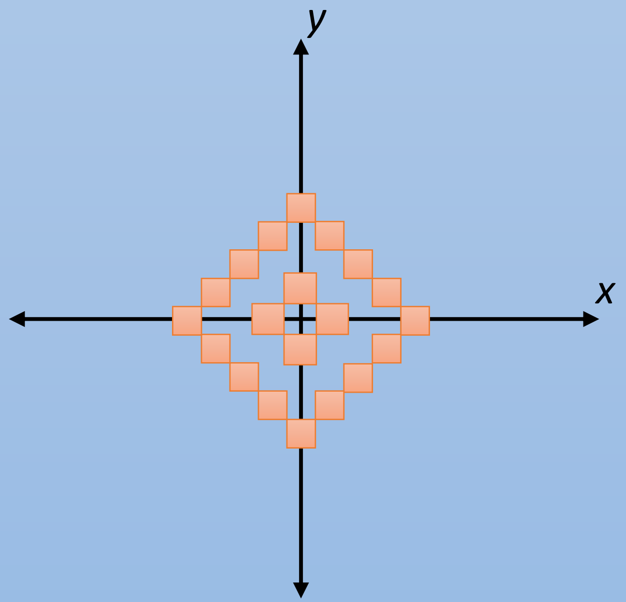

[Patitz, Summers, *Self-assembly of decidable sets*, UCNC 2008.]

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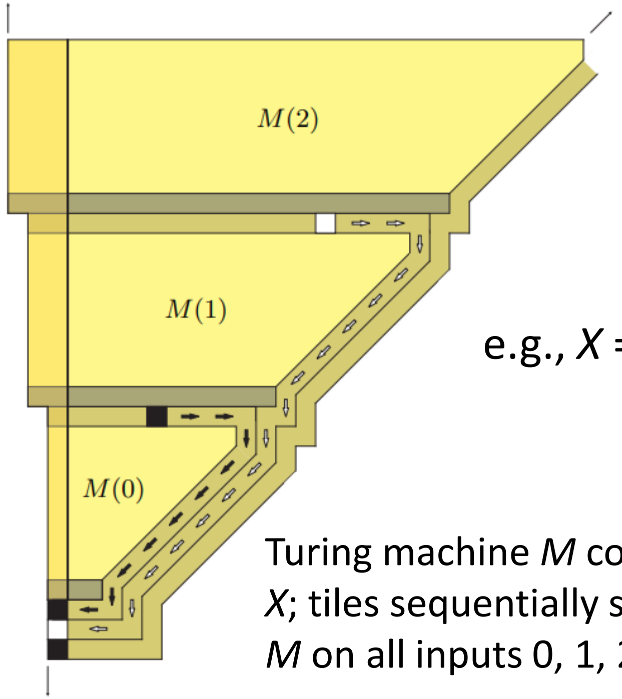

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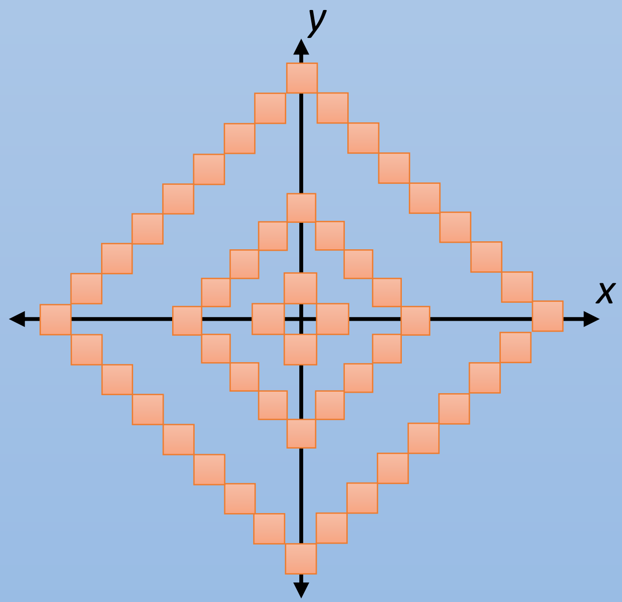

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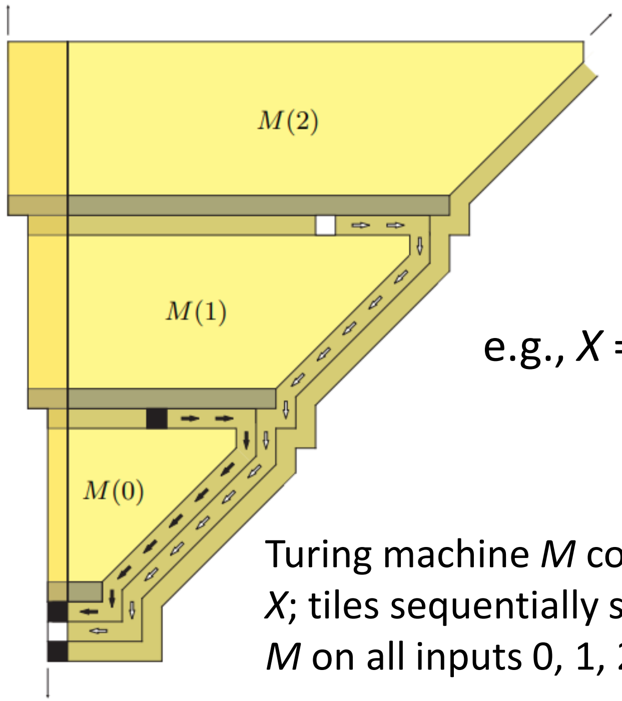

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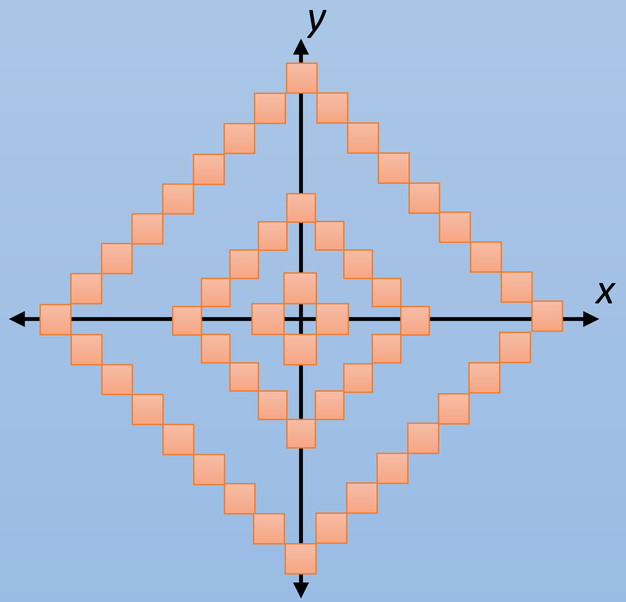

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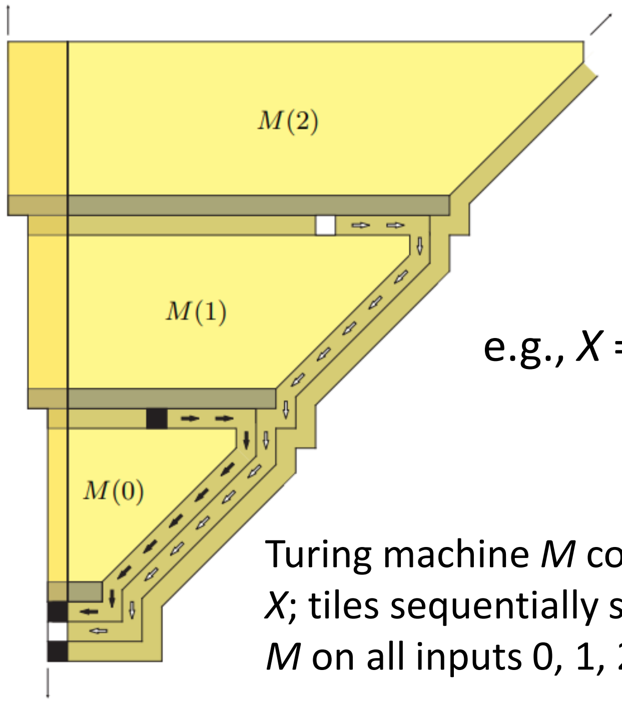

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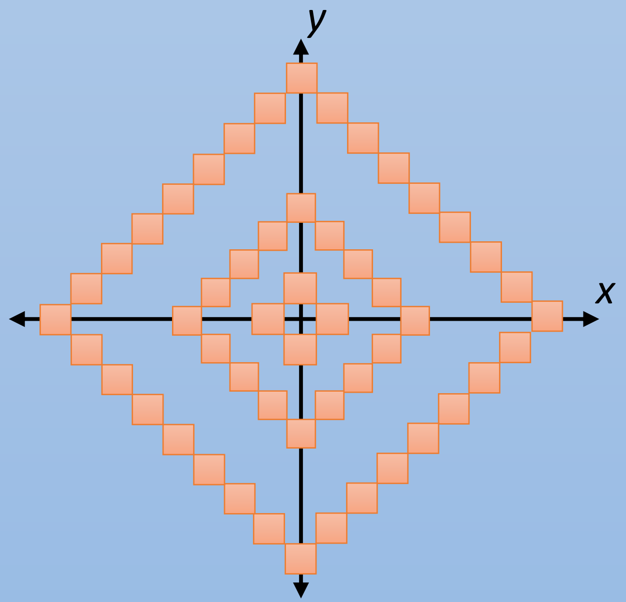

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5. This can be done in time $O(n^4)$ time (why?), a contradiction. **QED**

[Lathrop, Lutz, Patitz, Summers, *Computability and Complexity in Self-Assembly*, CiE 2008.]

Randomized self-assembly

Tile complexity of universal shape construction

- Recall: if we can have a seed structure encoding a shape S (in a binary string $x \in \{0,1\}^*$, in glues on one side), we can self-assemble some scaling S^c of S with $O(1)$ additional tile types that read and interpret x.

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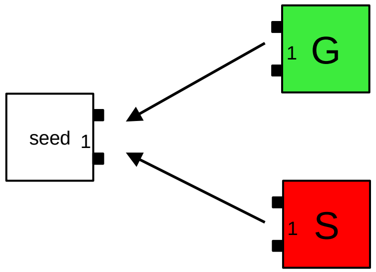
  - i.e., move the effort from designing new tile types to (*the plausibly simpler lab step of*) <u>altering concentrations</u> of existing tile types

Nondeterministic binding



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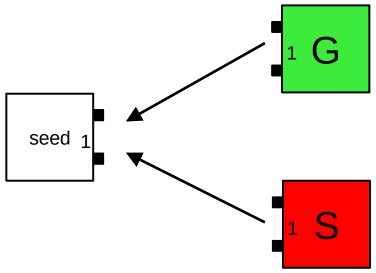
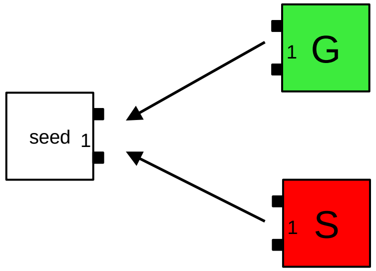


concentration 11

concentration 1

Nondeterministic binding



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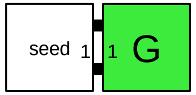
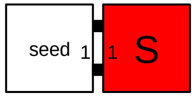
Pr[

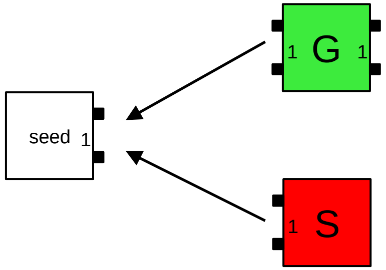
] = 11/12

Pr[

] = 1/12

Programming polymer length with concentrations

[Becker, Rapaport, Rémila, *FSTTCS* 2006]



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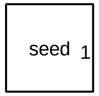

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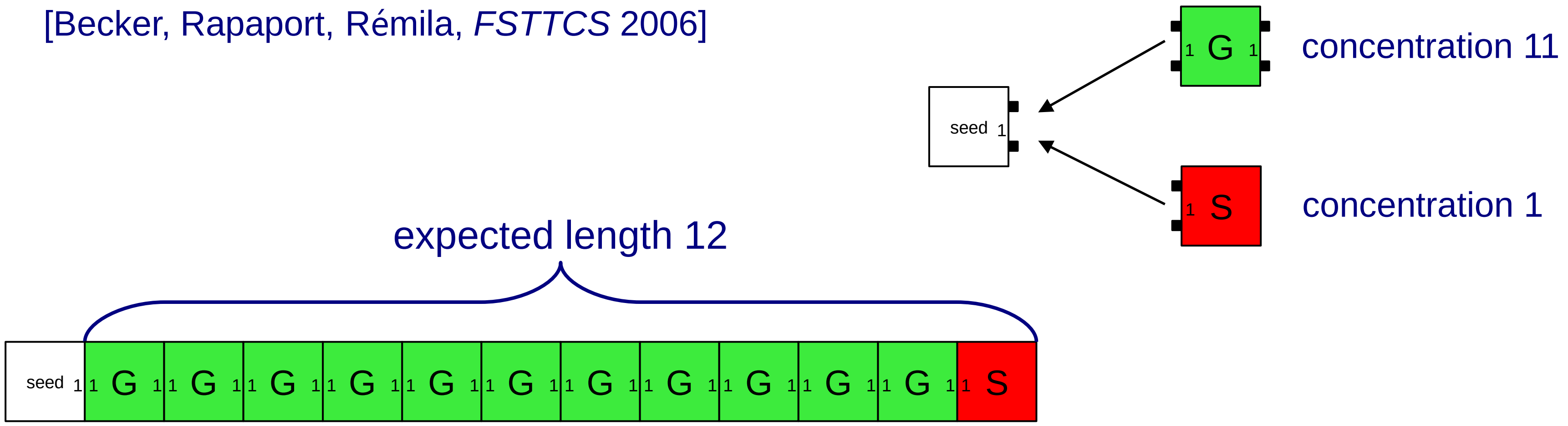

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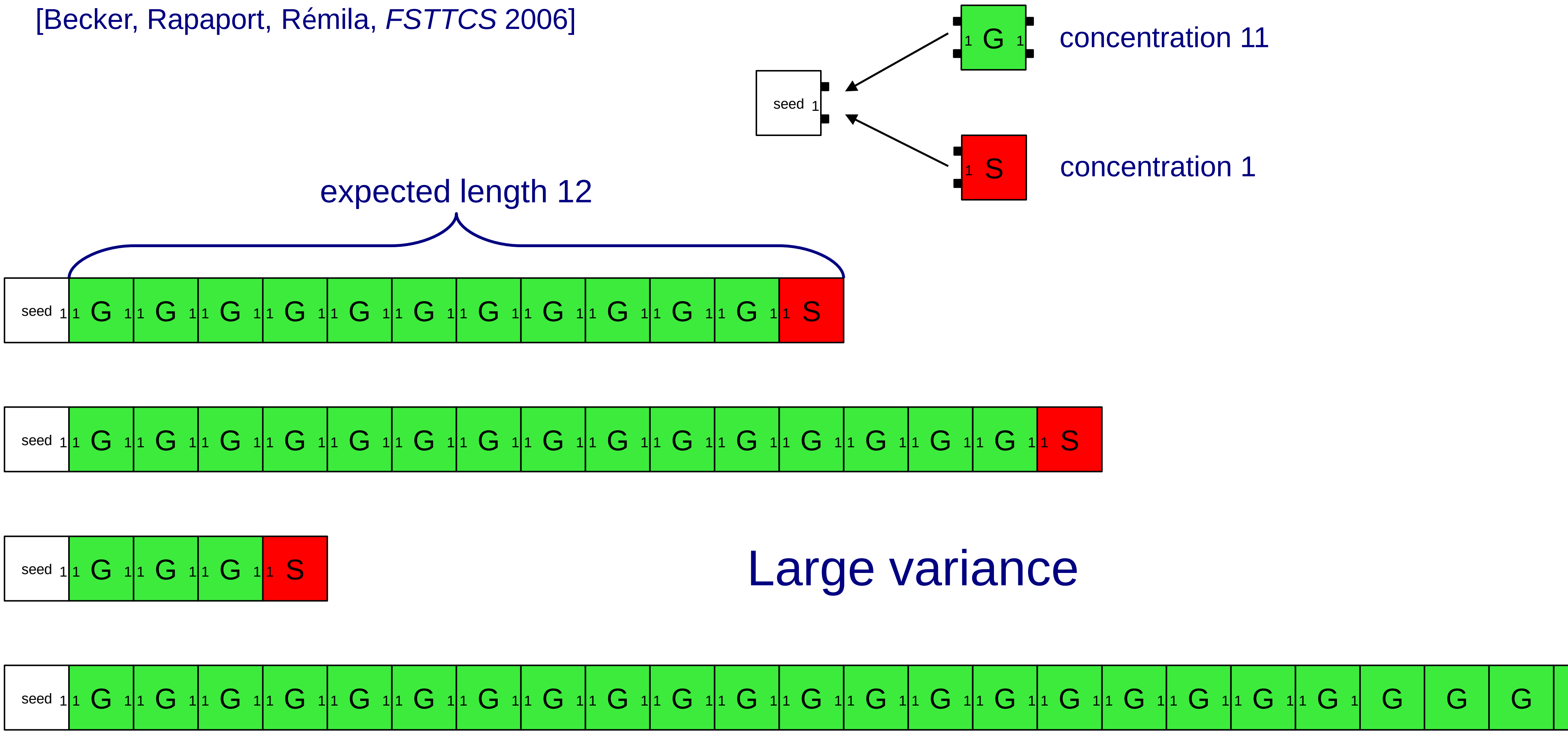
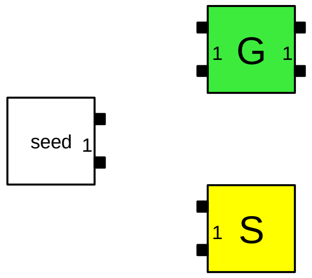


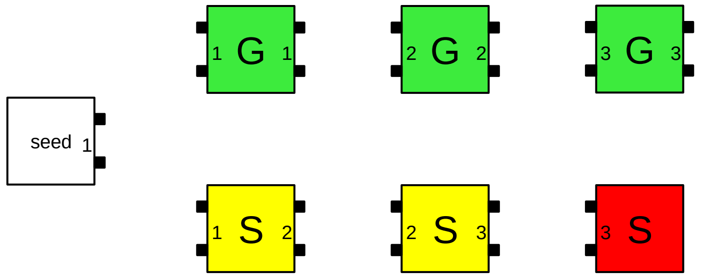
Programming polymer length (improved)



concentration 3

concentration 1

Programming polymer length (improved)



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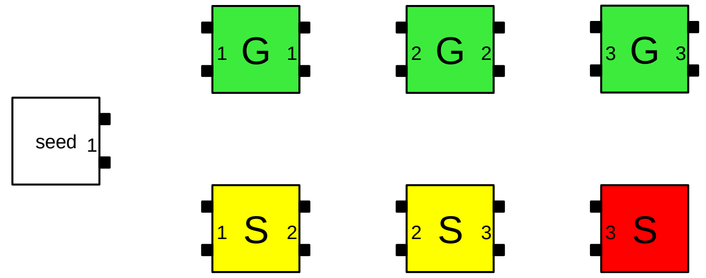
3 "stages", each of expected length 4

Programming polymer length (improved)



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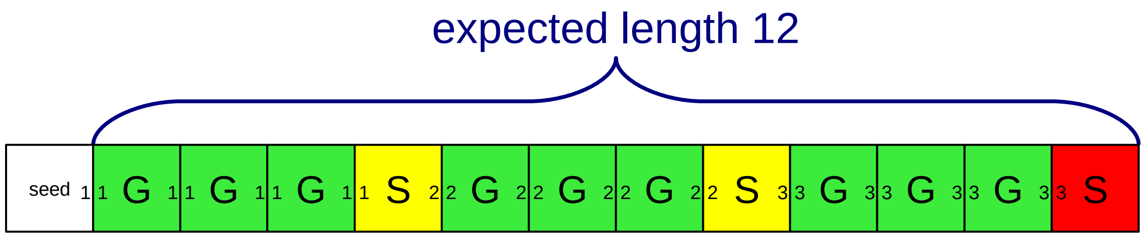

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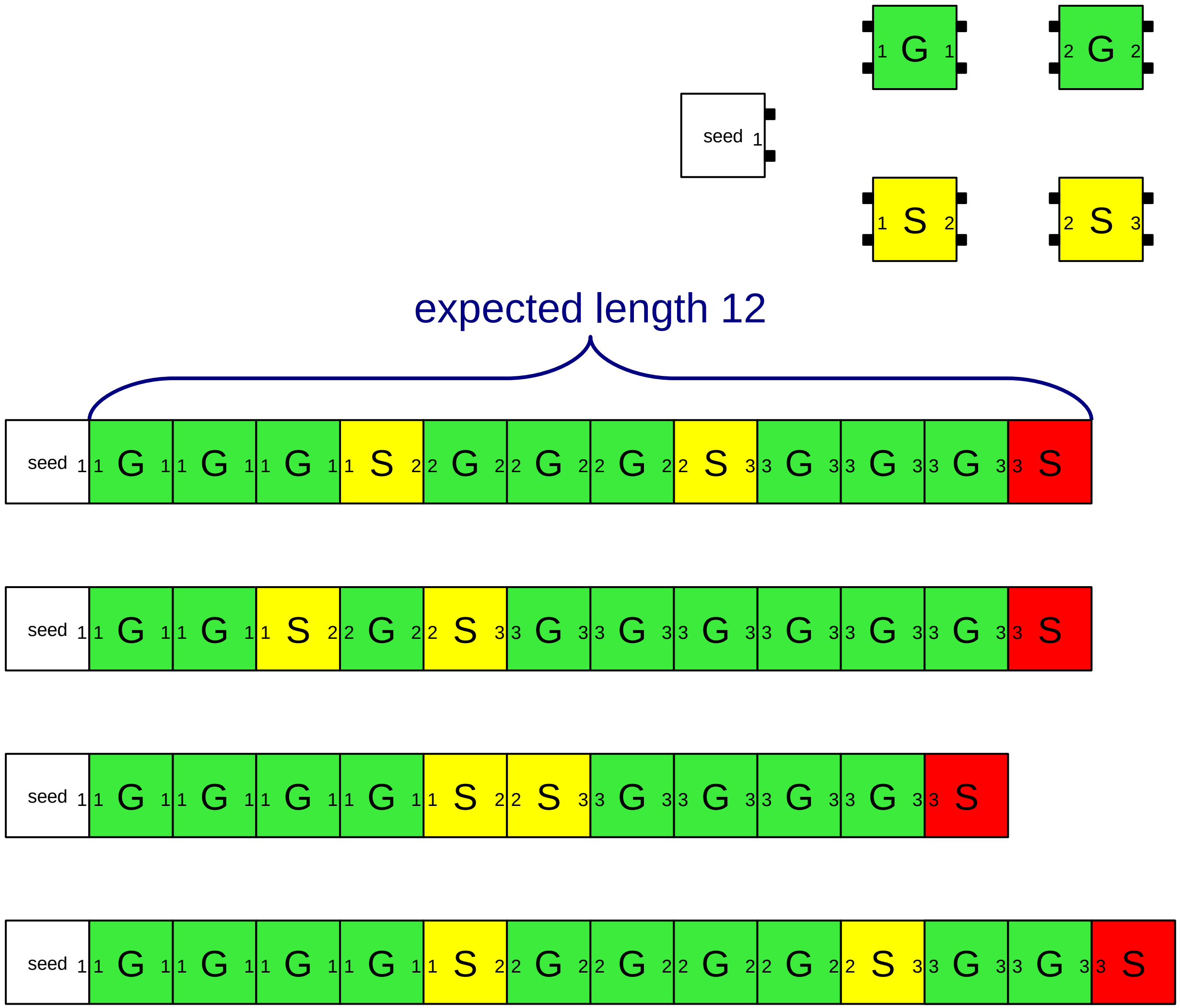

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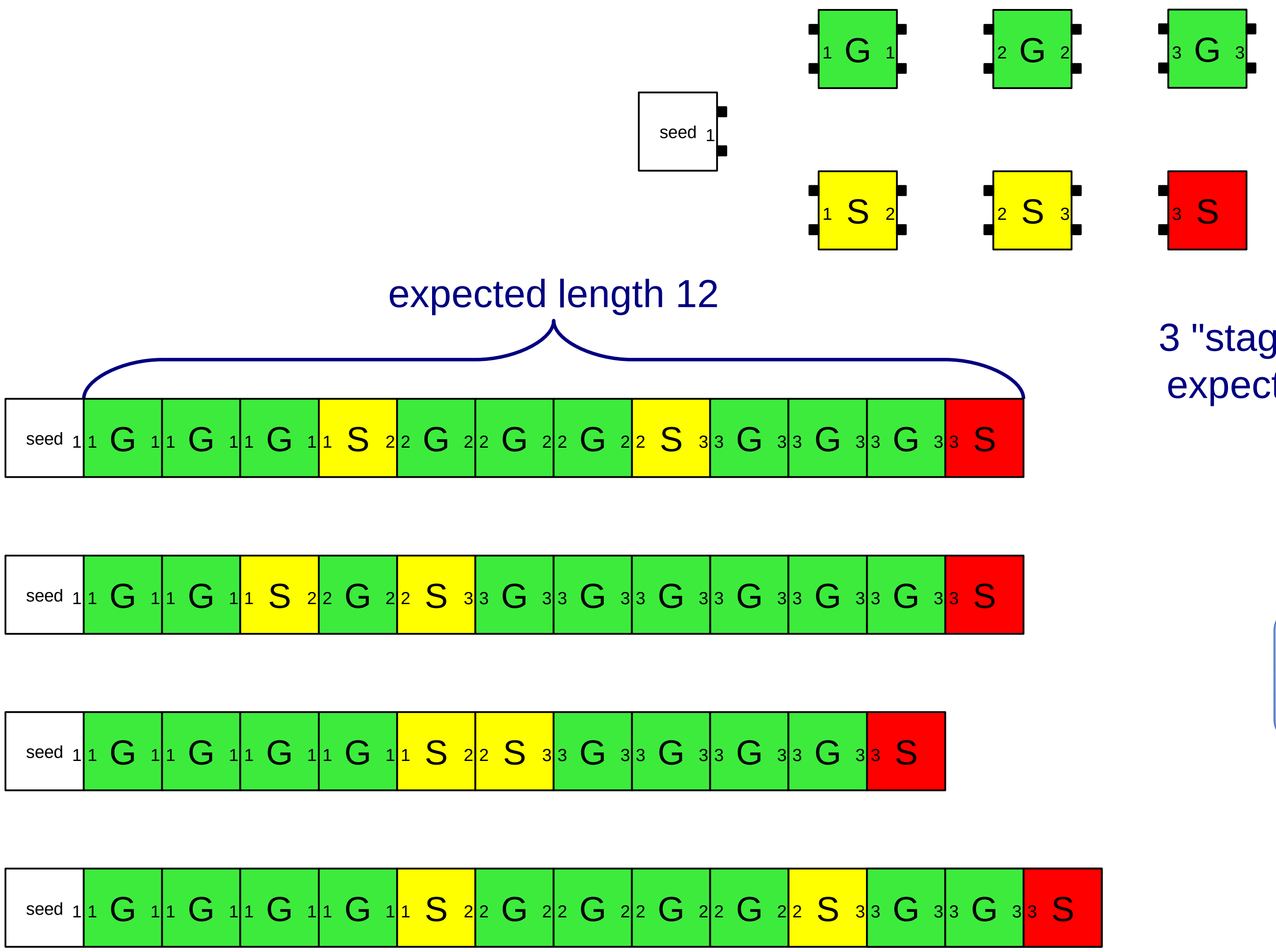

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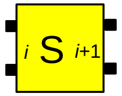
Lower variance…
how much lower?

Bounding the probability the length deviates much from its mean

- r total stages, each with Pr[next tile 

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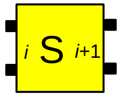
- *r* total stages, each with Pr[next tile 

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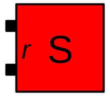
- Let **L**(*r*,*p*) = total length; number of tile attachments until attaching 

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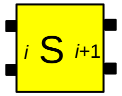
- r total stages, each with Pr[next tile 

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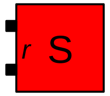
- Let $\mathbf{L}(r,p)$ = total length; number of tile attachments until attaching 

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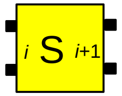
- *r* total stages, each with Pr[next tile 

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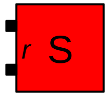
- Let **L**(*r*,*p*) = total length; number of tile attachments until attaching 

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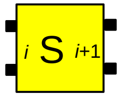
- *r* total stages, each with Pr[next tile 

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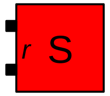
- Let **L**(*r*,*p*) = total length; number of tile attachments until attaching 

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flipping a coin until the *r*'th heads requires $\leq$ *n* flips $\Leftrightarrow$ flipping a coin *n* times results in $\geq$ *r* heads

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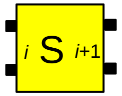
- r total stages, each with Pr[next tile 

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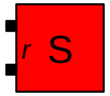
- Let $\mathbf{L}(r,p)$ = total length; number of tile attachments until attaching 

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- for any n,r,p: $\Pr[\mathbf{L}(r,p) \leq n] = \Pr[\mathbf{B}(n,p) \geq r]$

flipping a coin until the r'th heads requires $\leq n$ flips $\Leftrightarrow$ flipping a coin n times results in $\geq r$ heads

- similarly, $\Pr[\mathbf{L}(r,p) \geq n] = \Pr[\mathbf{B}(n,p) \leq r]$

Chernoff bound

Chernoff bound: For a binomial random variable $\mathbf{B}(n,p)$ (recall $E[\mathbf{B}(n,p)] = np$), and for any $0 < \delta < 1$,

$\Pr[\mathbf{B}(n,p) > (1+\delta)np] < \exp(-\delta^2 np/3)$

$\Pr[\mathbf{B}(n,p) < (1-\delta)np] < \exp(-\delta^2 np/2)$

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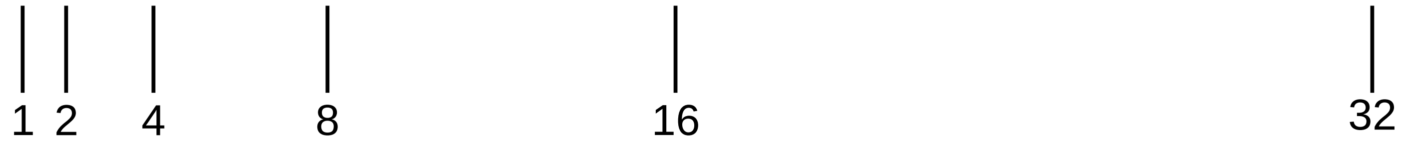
Let $\delta \approx 0.27$ and set p such that $r/p(1-\delta) = 2^k$.
Let $\delta' \approx 0.44$: then $r/p(1+\delta') \approx 2^{k-1}$.
Applying this to our setting gives
$\Pr[\mathbf{L}(r,p)$ is not between 2^{k-1} and $2^k] < 2\cdot 0.9421^r$

Programming polymer length (improved)

if r = 90 stages, expected length midway in $[2^{k-1}, 2^k)$

with probability > 99%, **actual** length in $[2^{k-1}, 2^k)$



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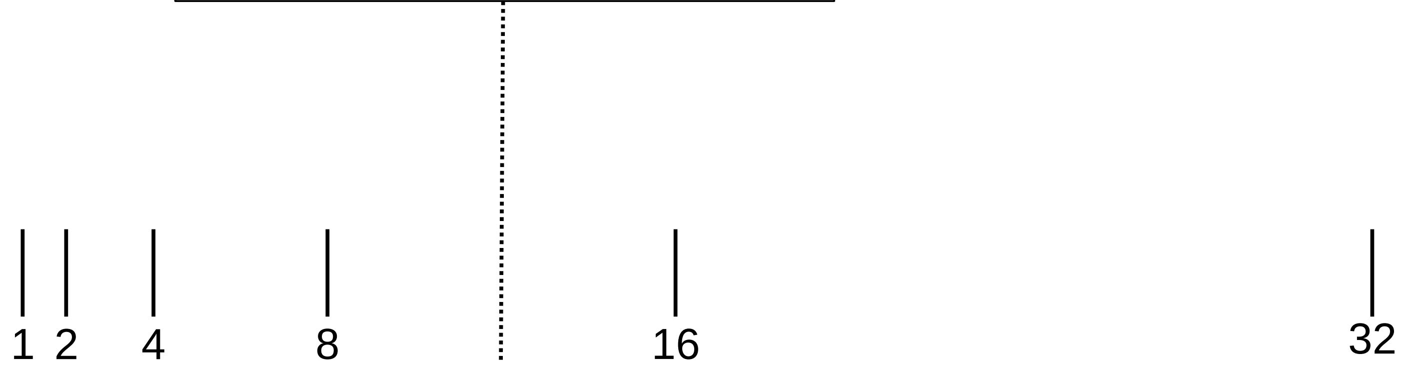
[G] ≈ 7   [S] = [S] ≈ 2



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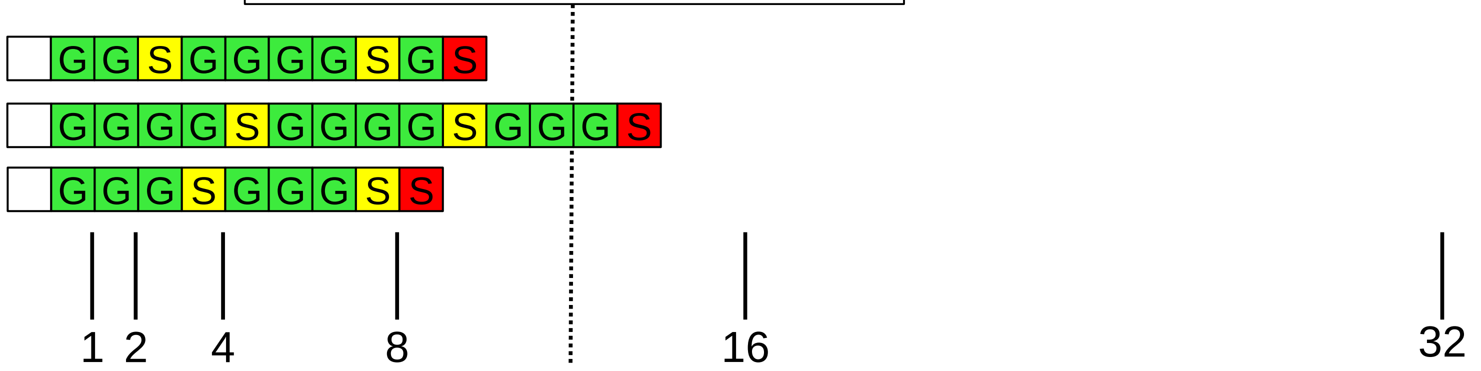

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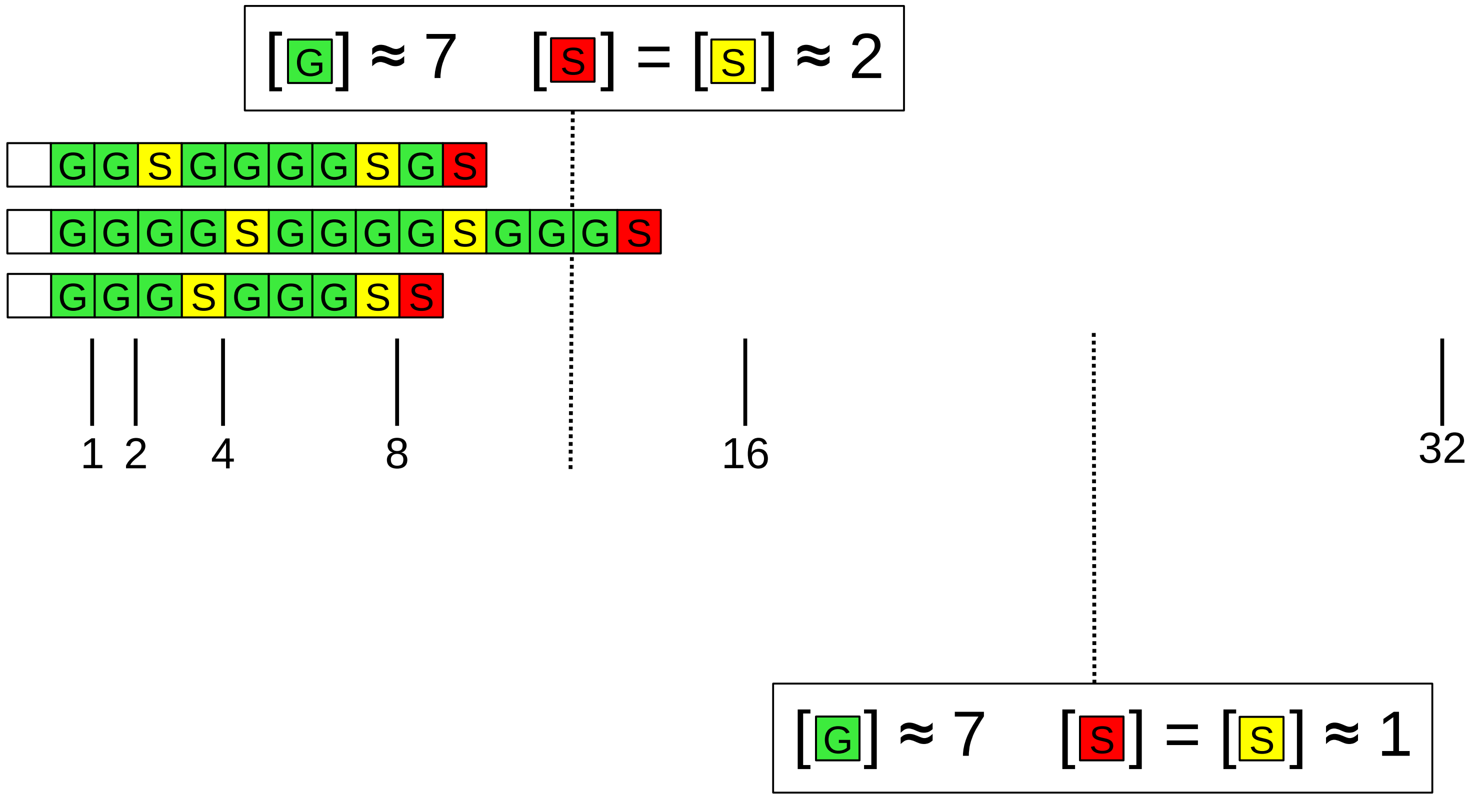

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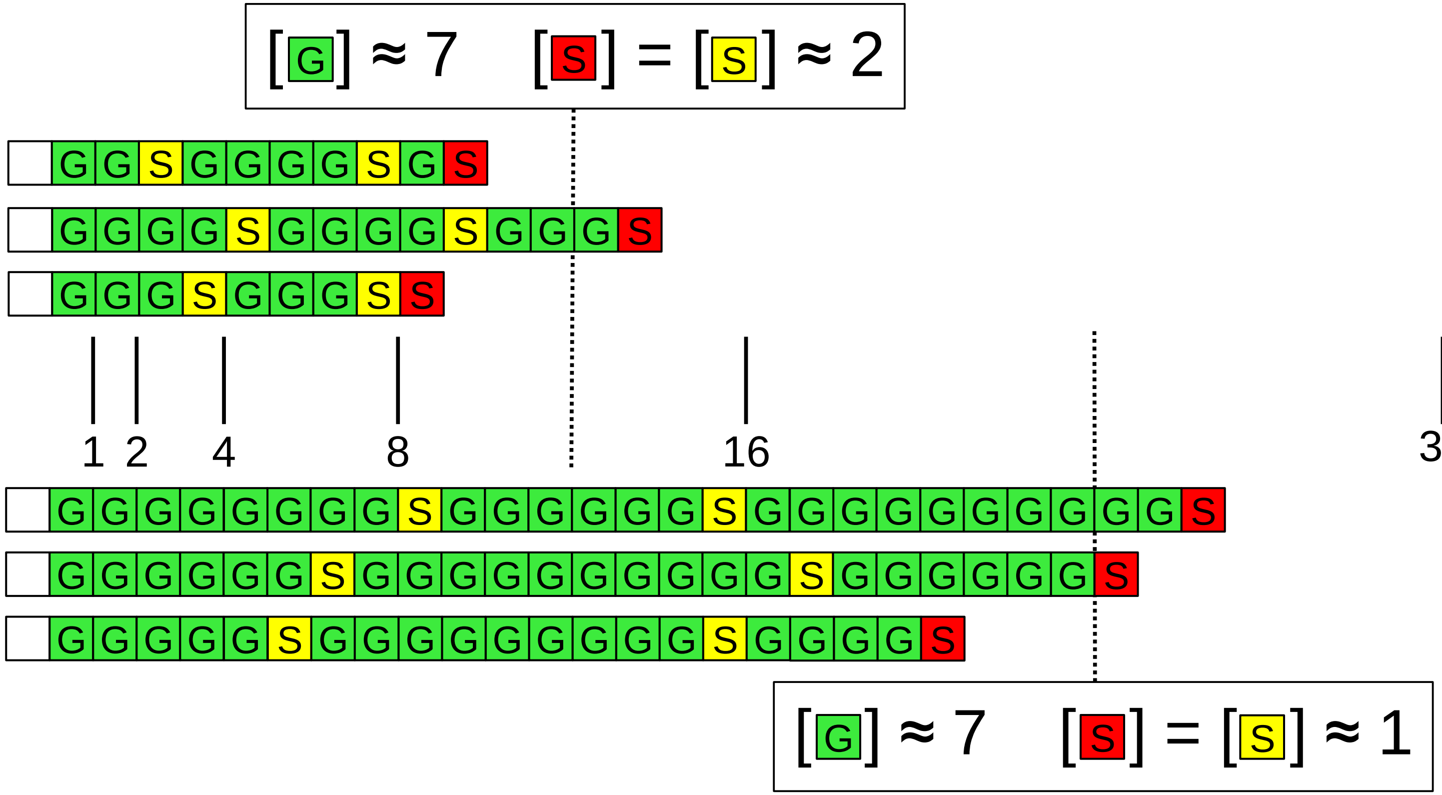

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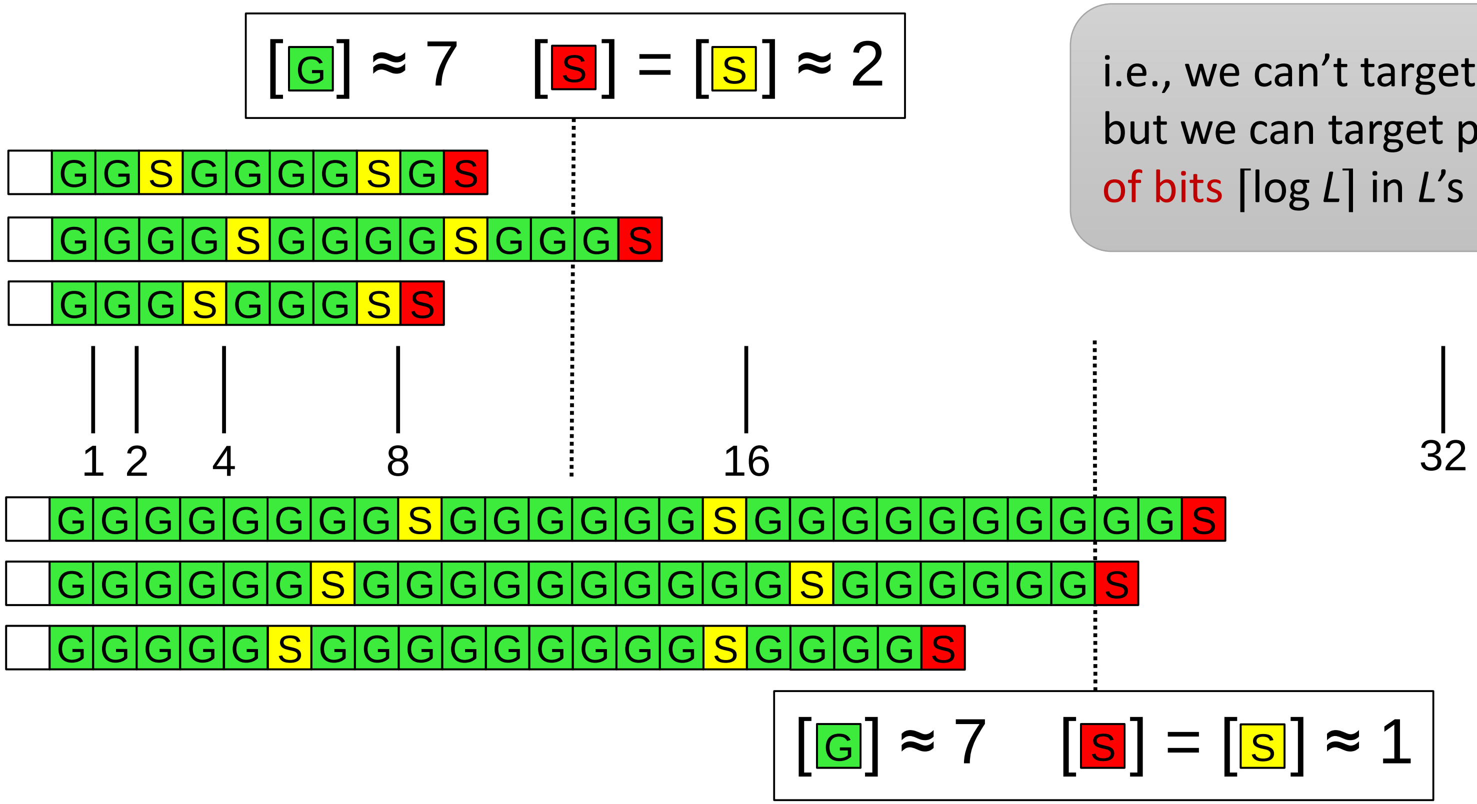

i.e., we can't target a precise length L, but we can target precisely the number of bits $\lceil \log L \rceil$ in L's binary expansion.

Programming polymer length 2^k precisely

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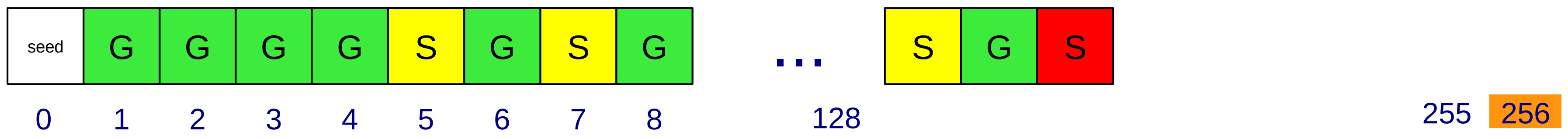
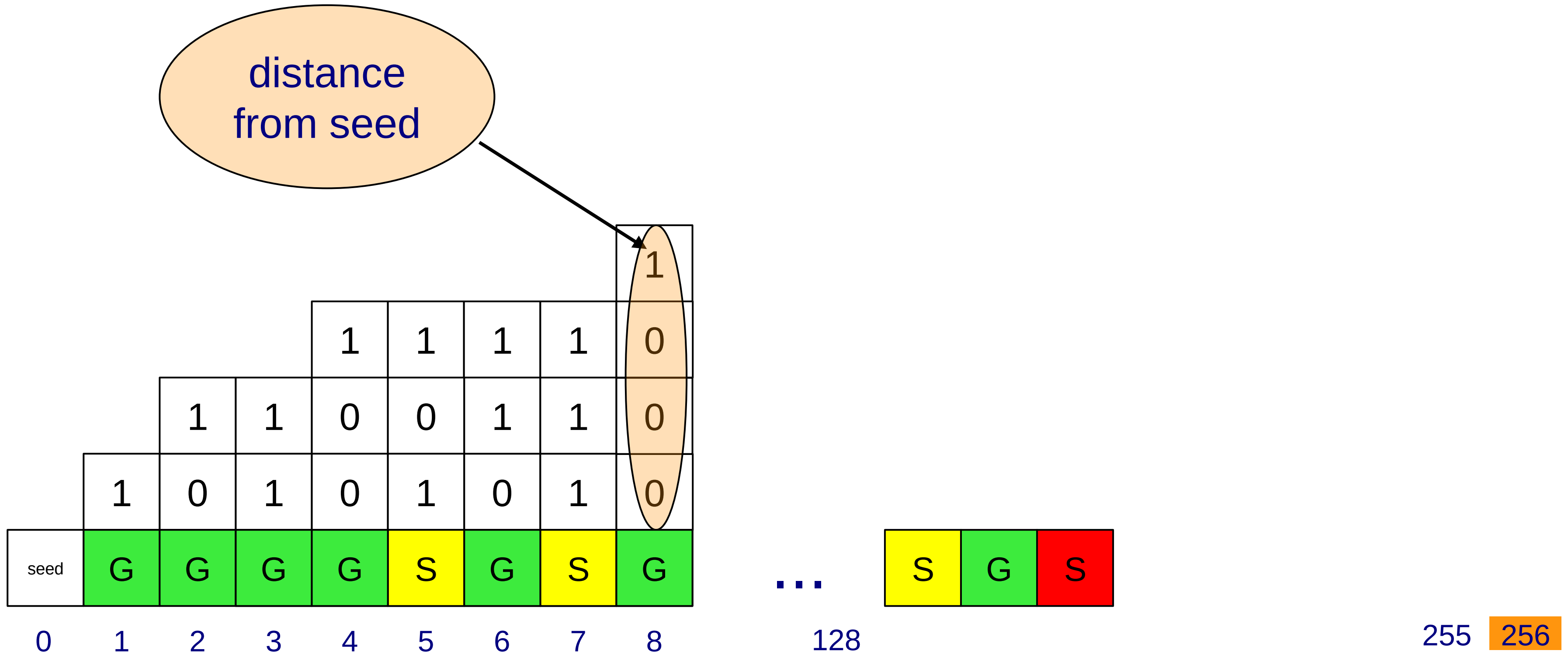


Programming polymer length 2^k precisely



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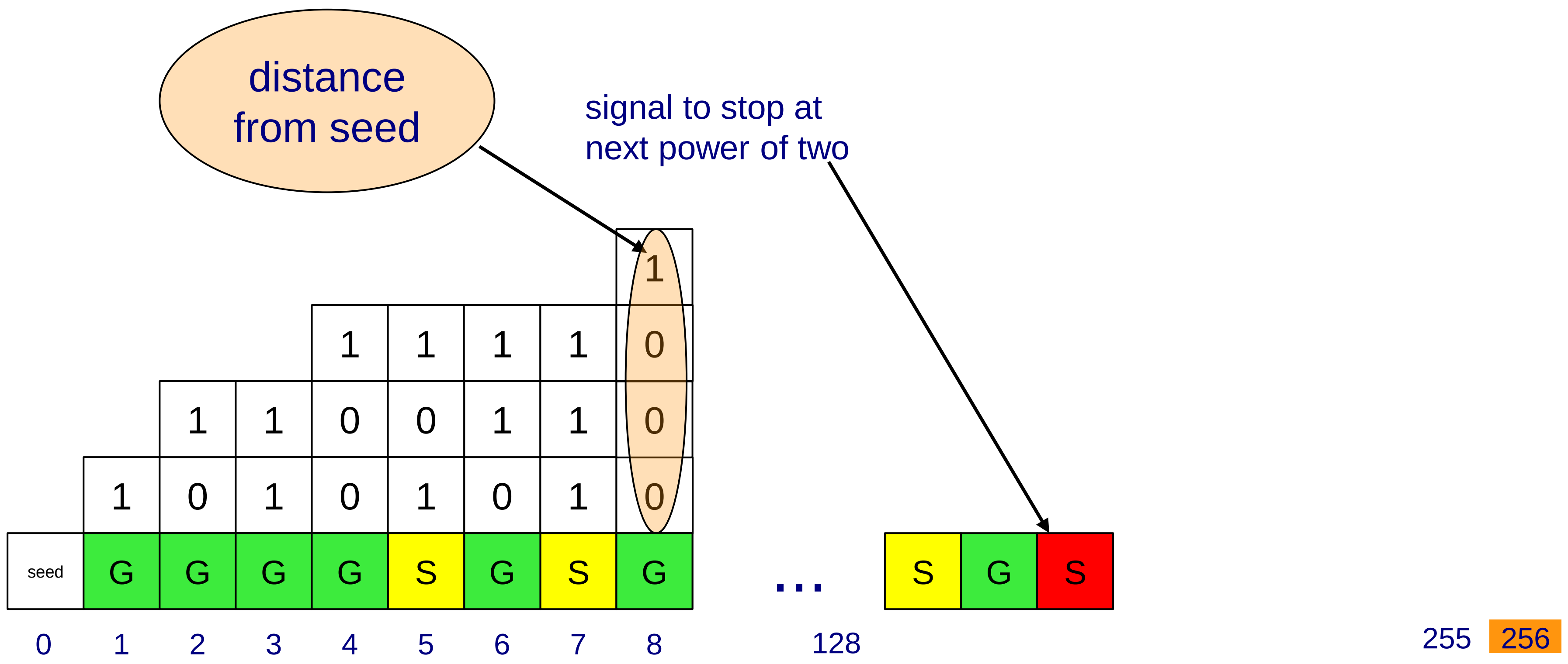

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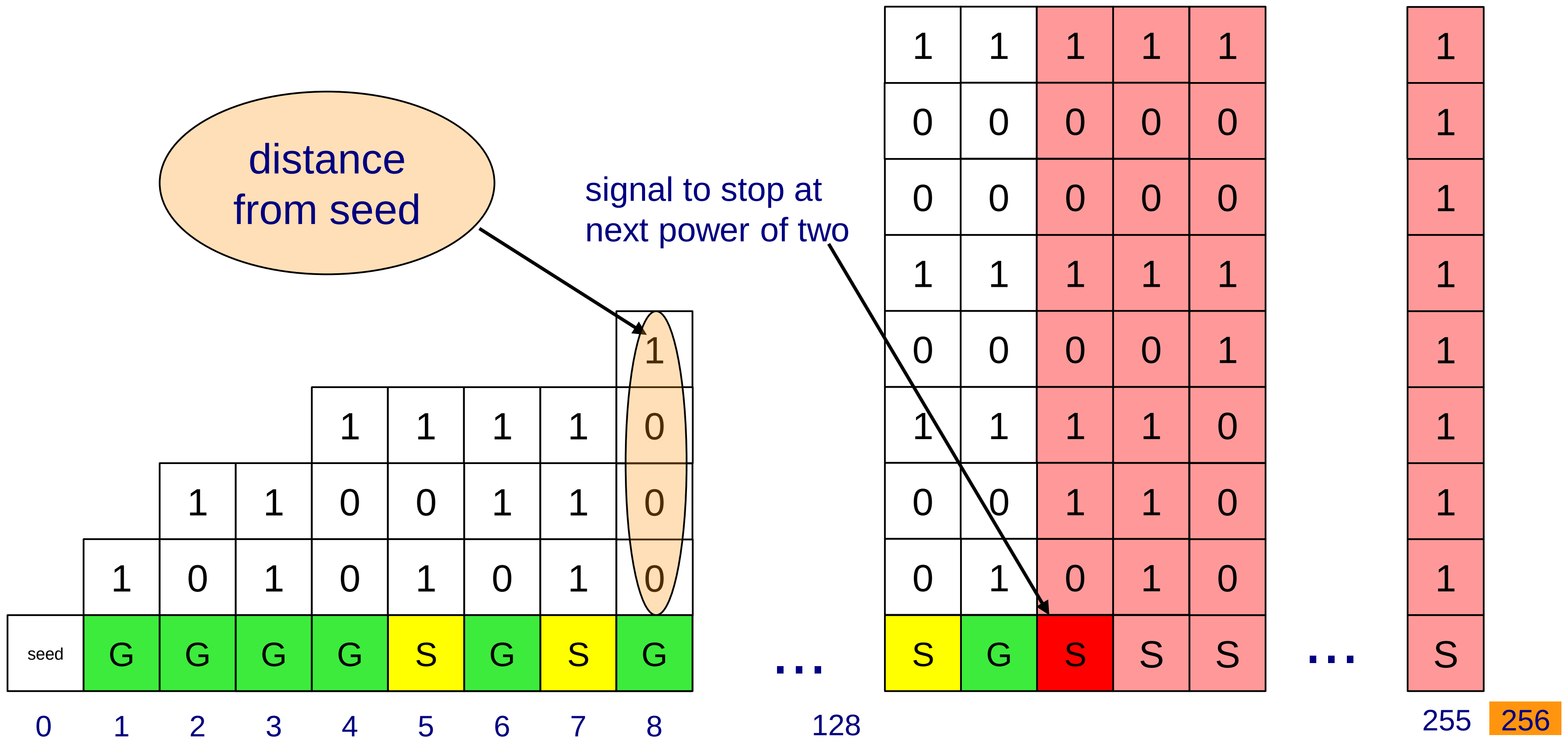

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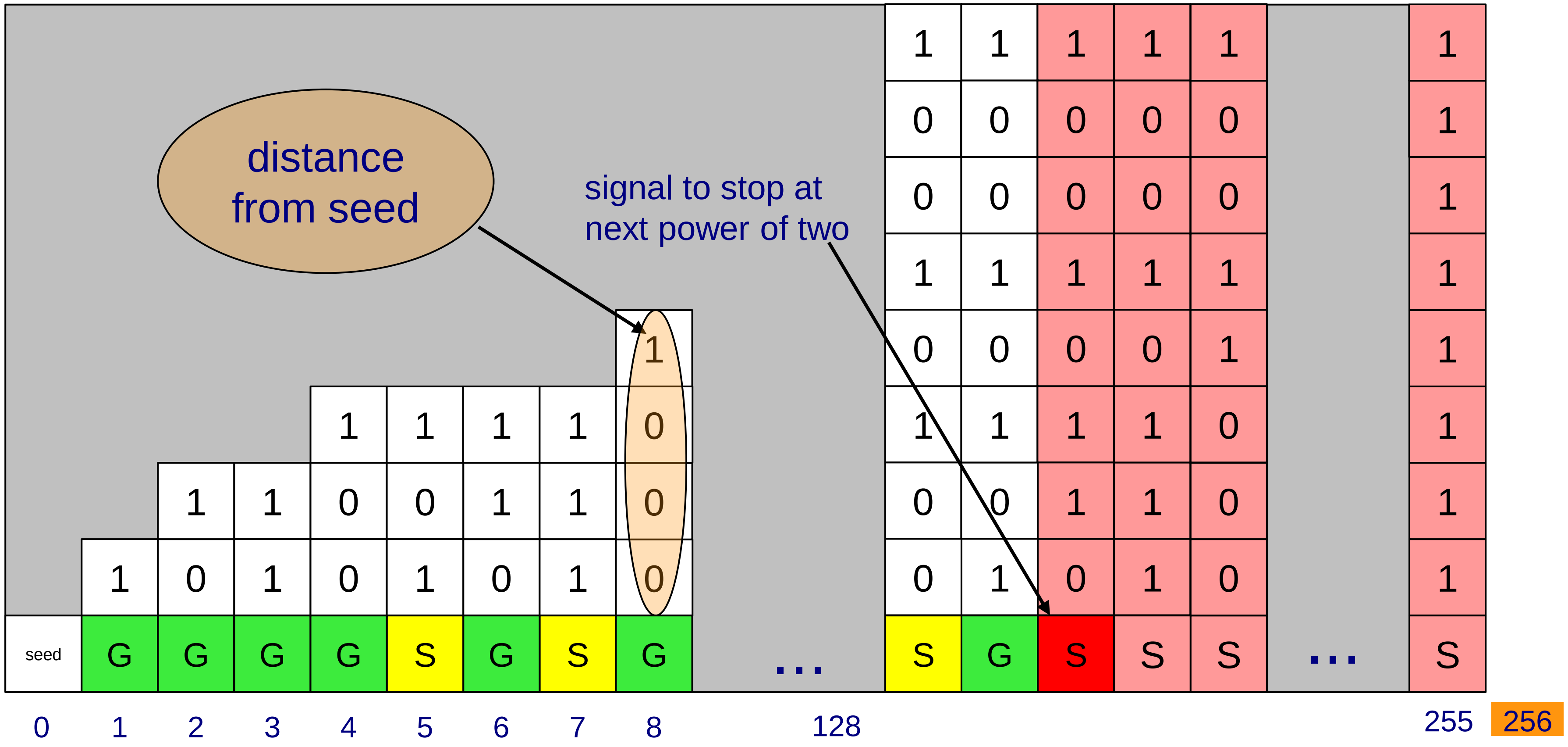
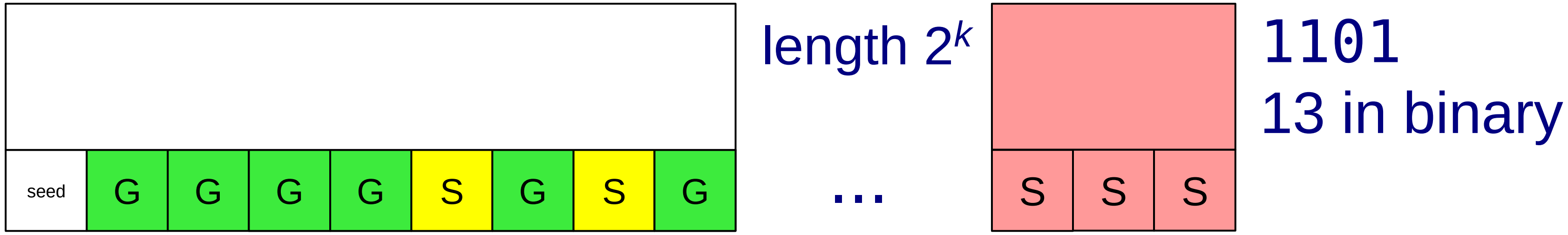


Programming a binary string

`1101`

13 in binary

Programming a binary string



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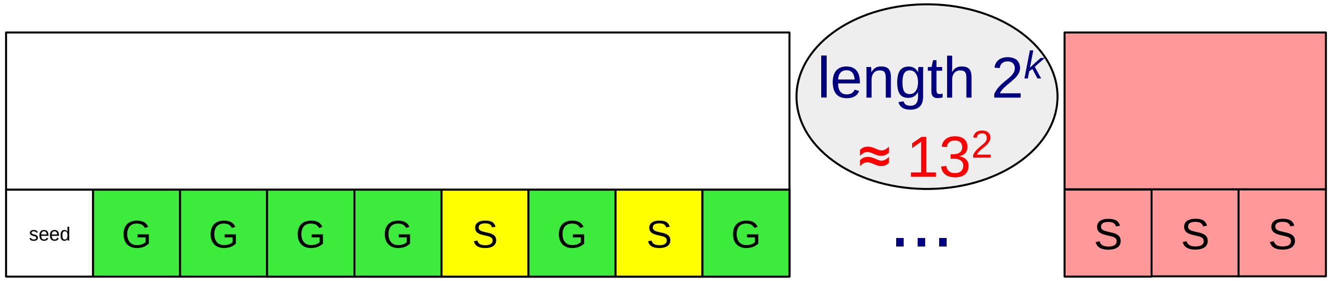

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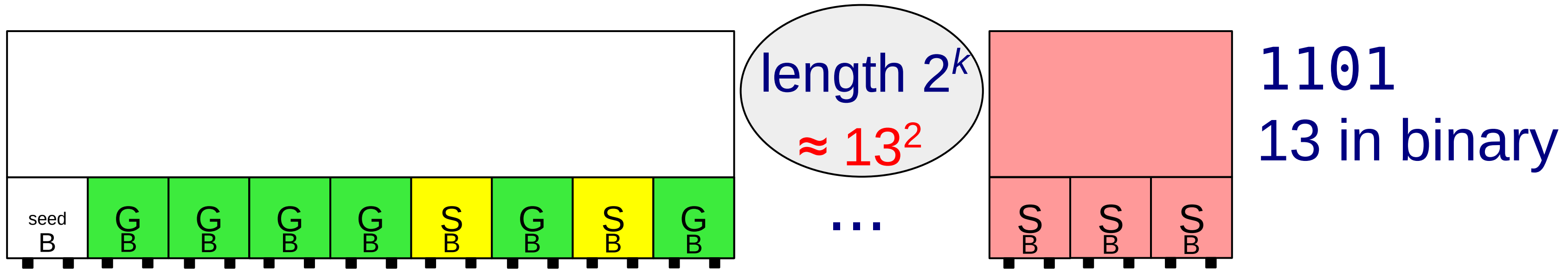

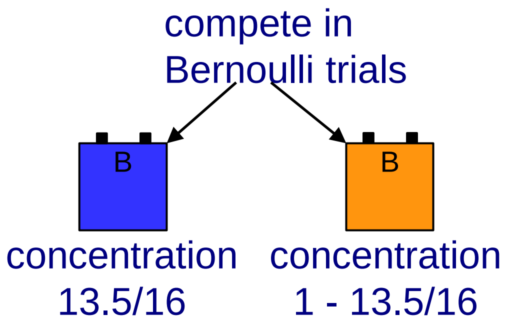

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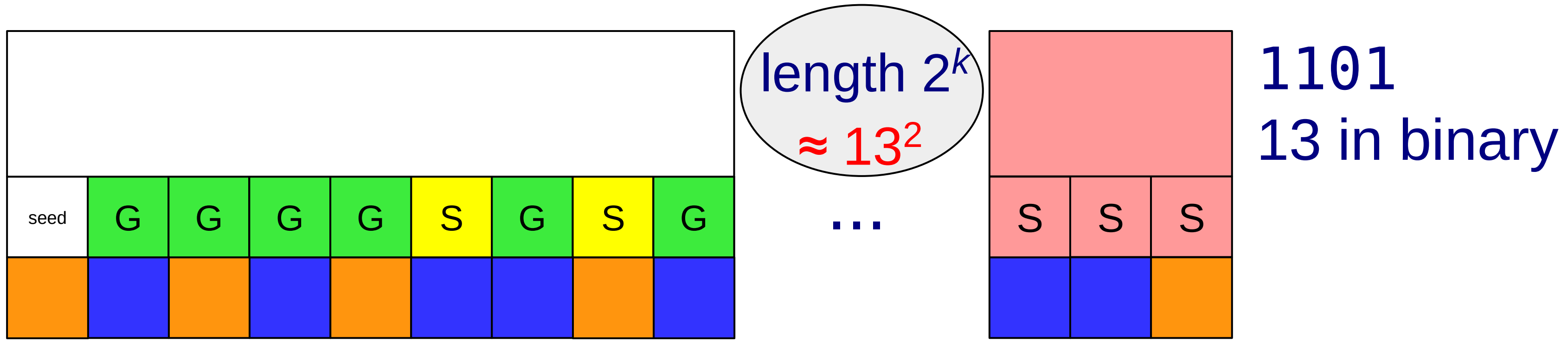

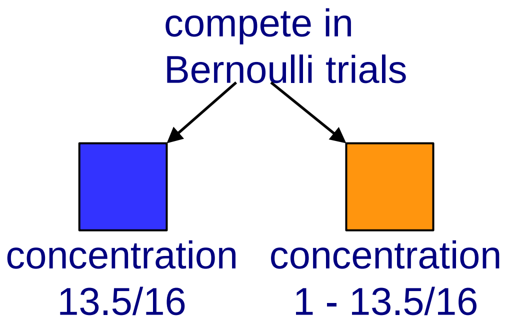

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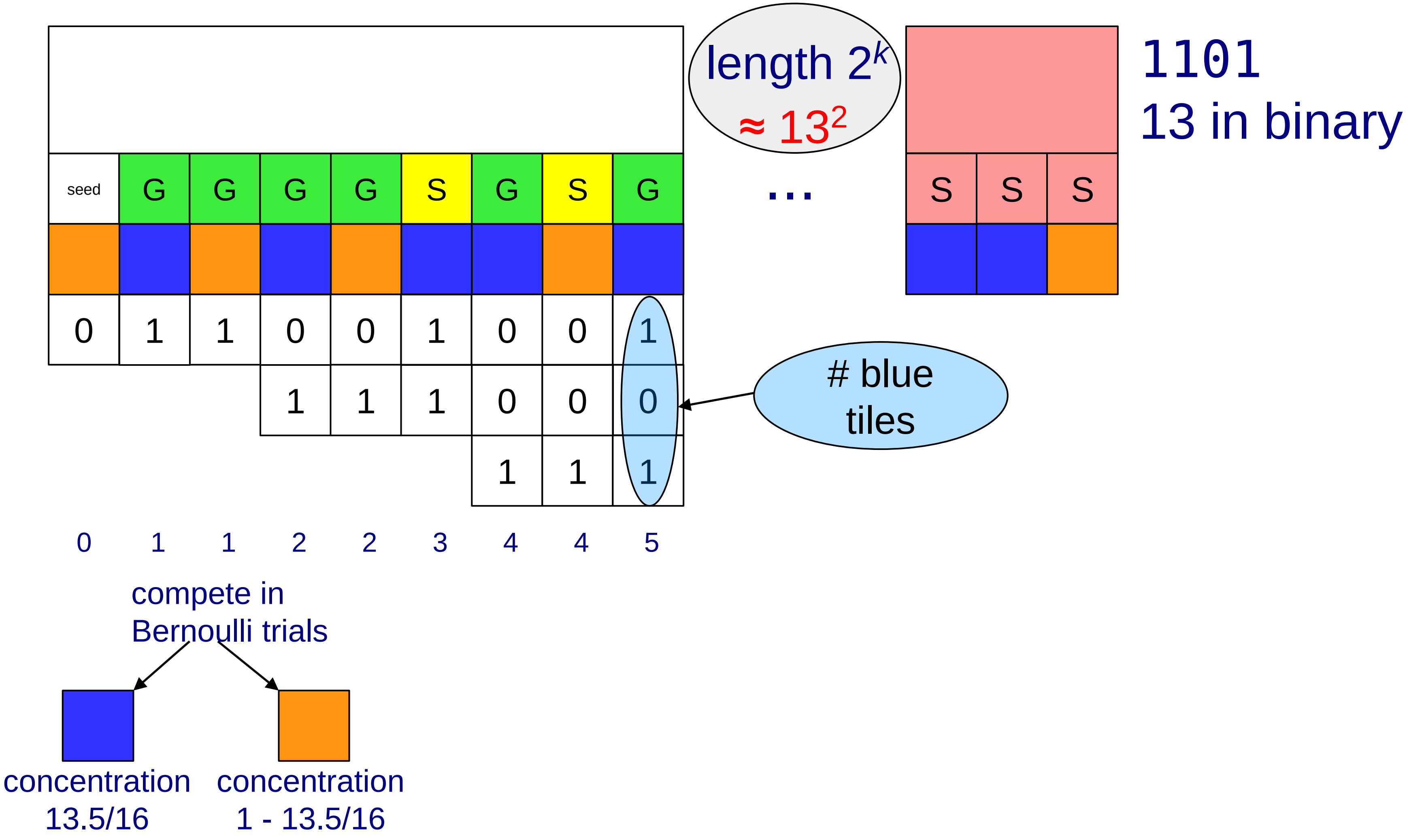

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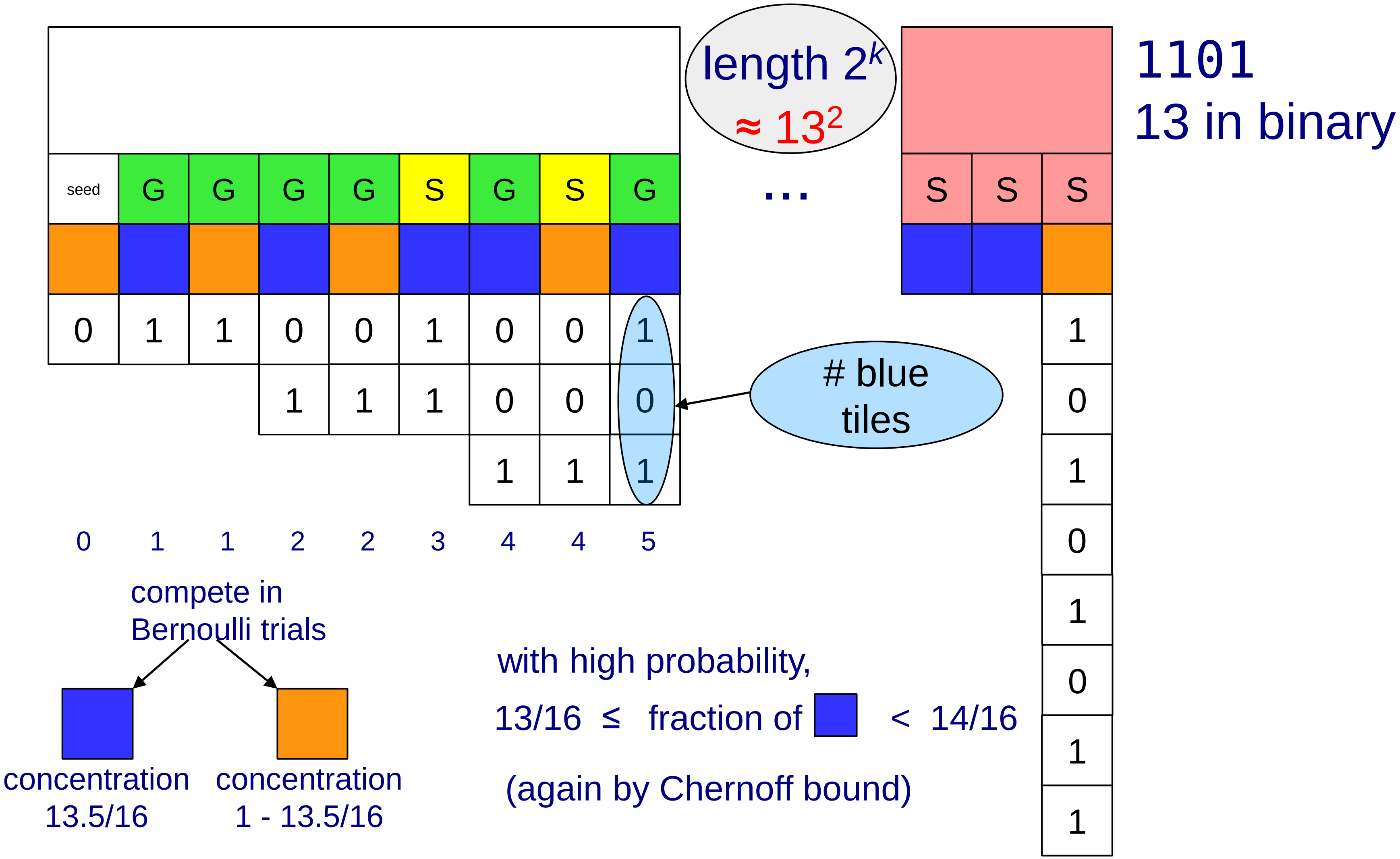

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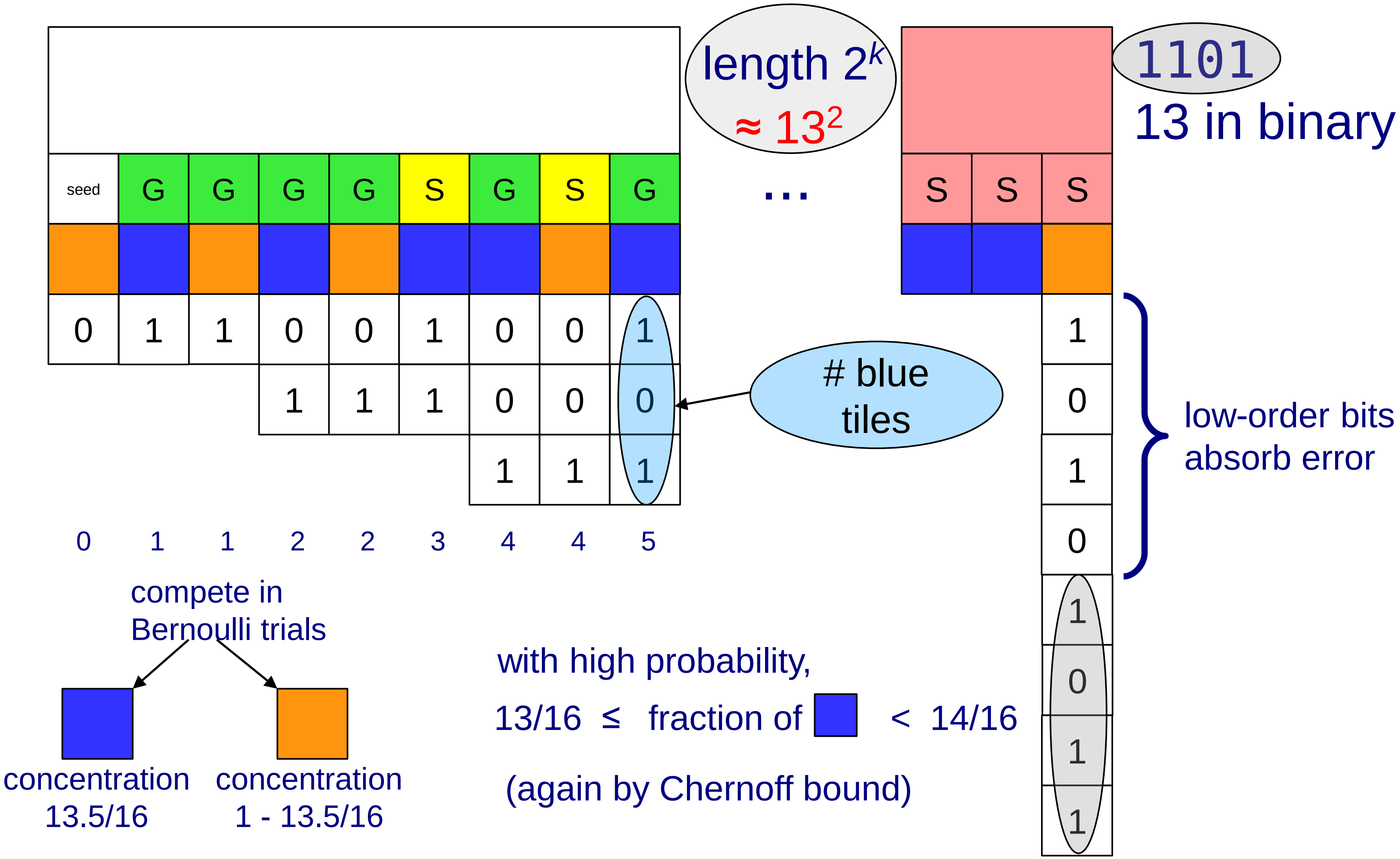

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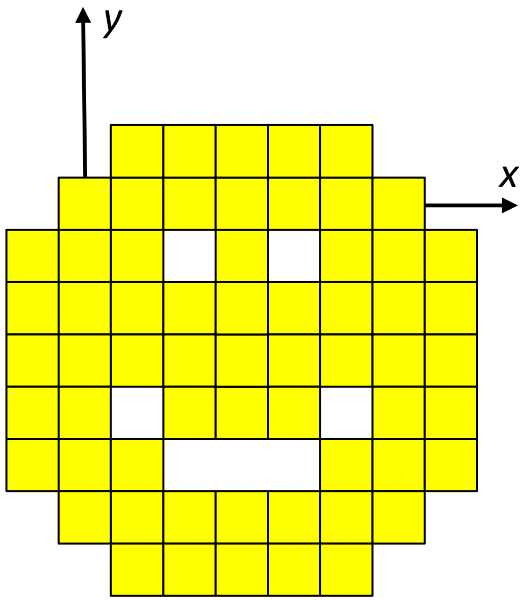

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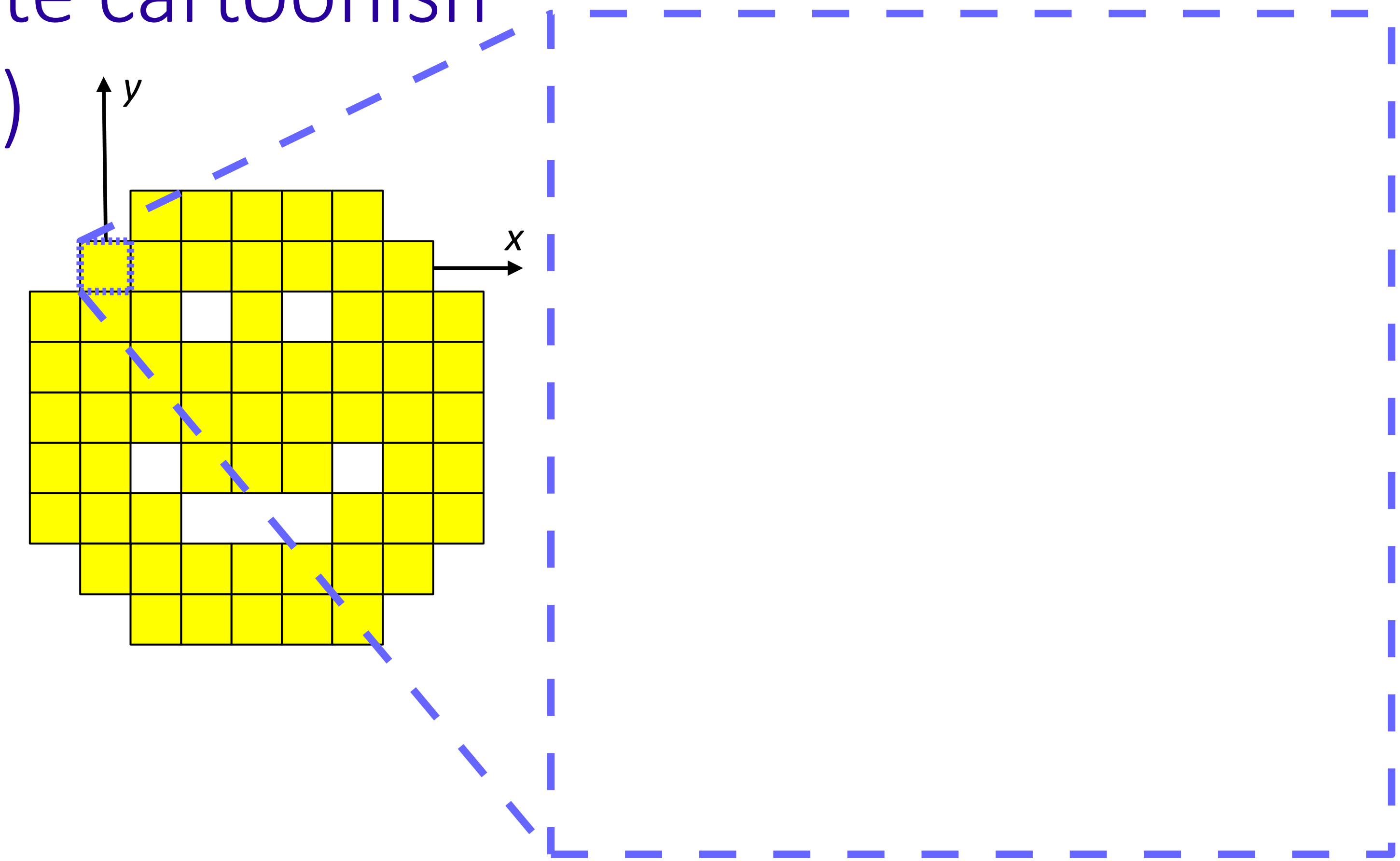

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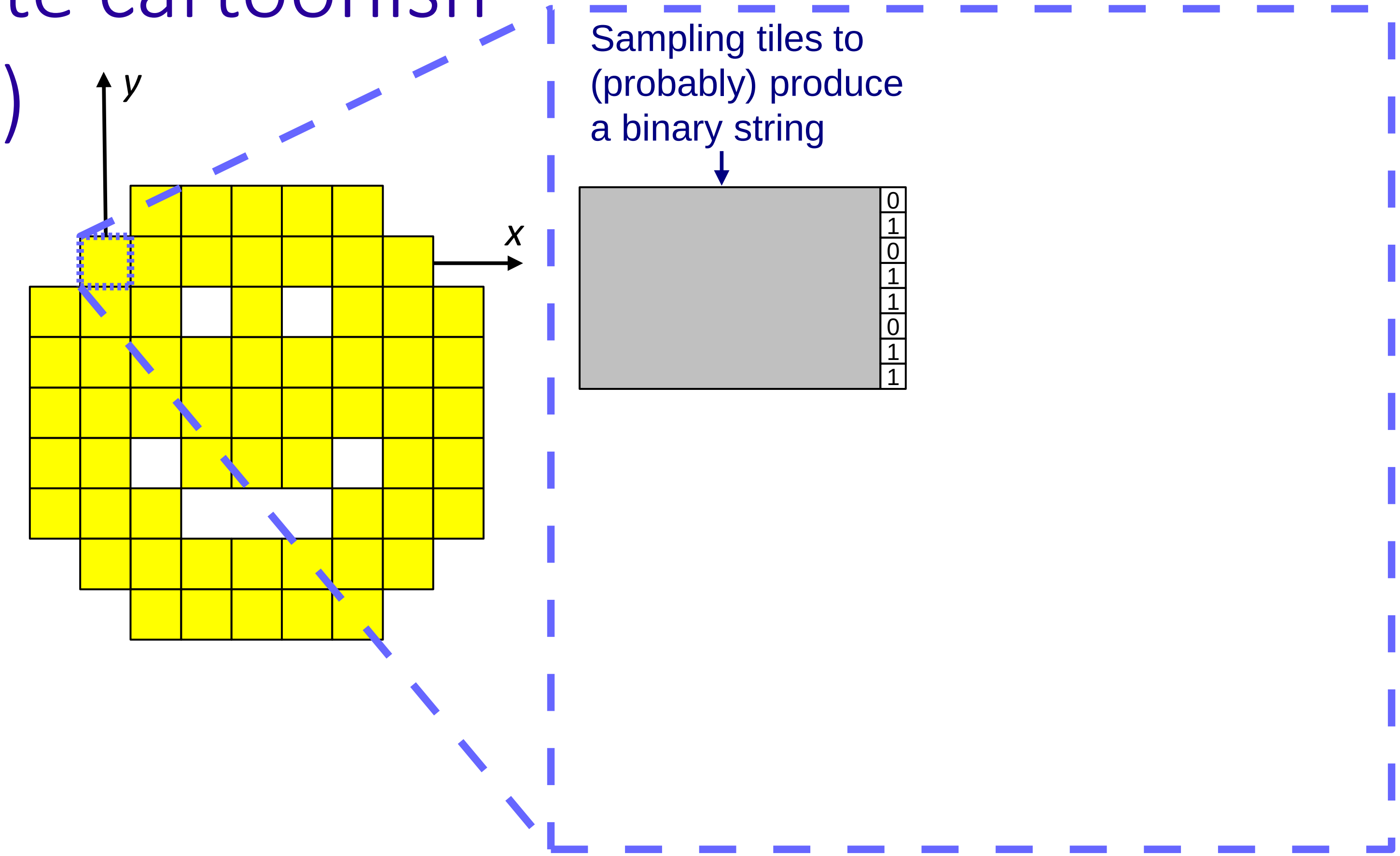

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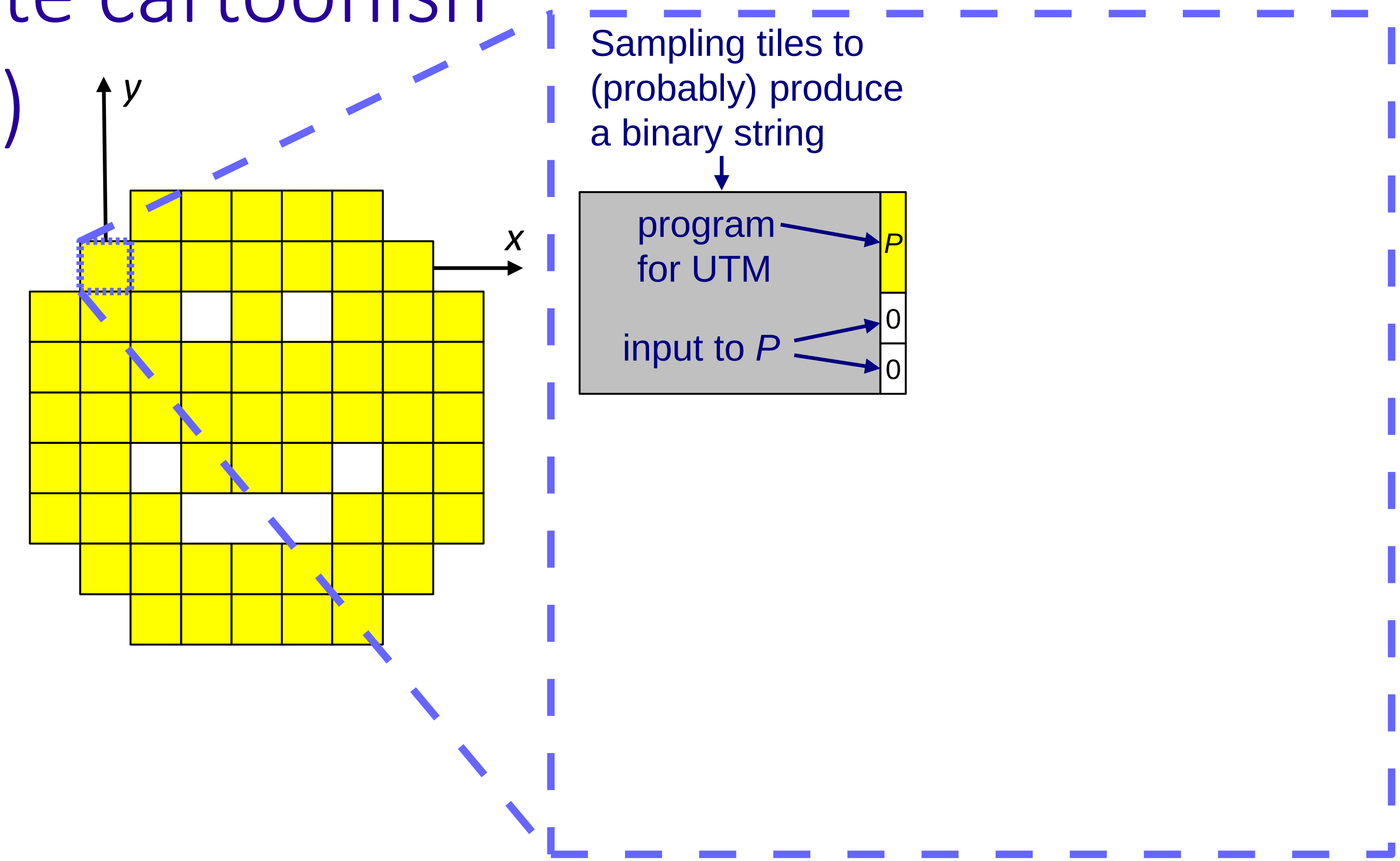

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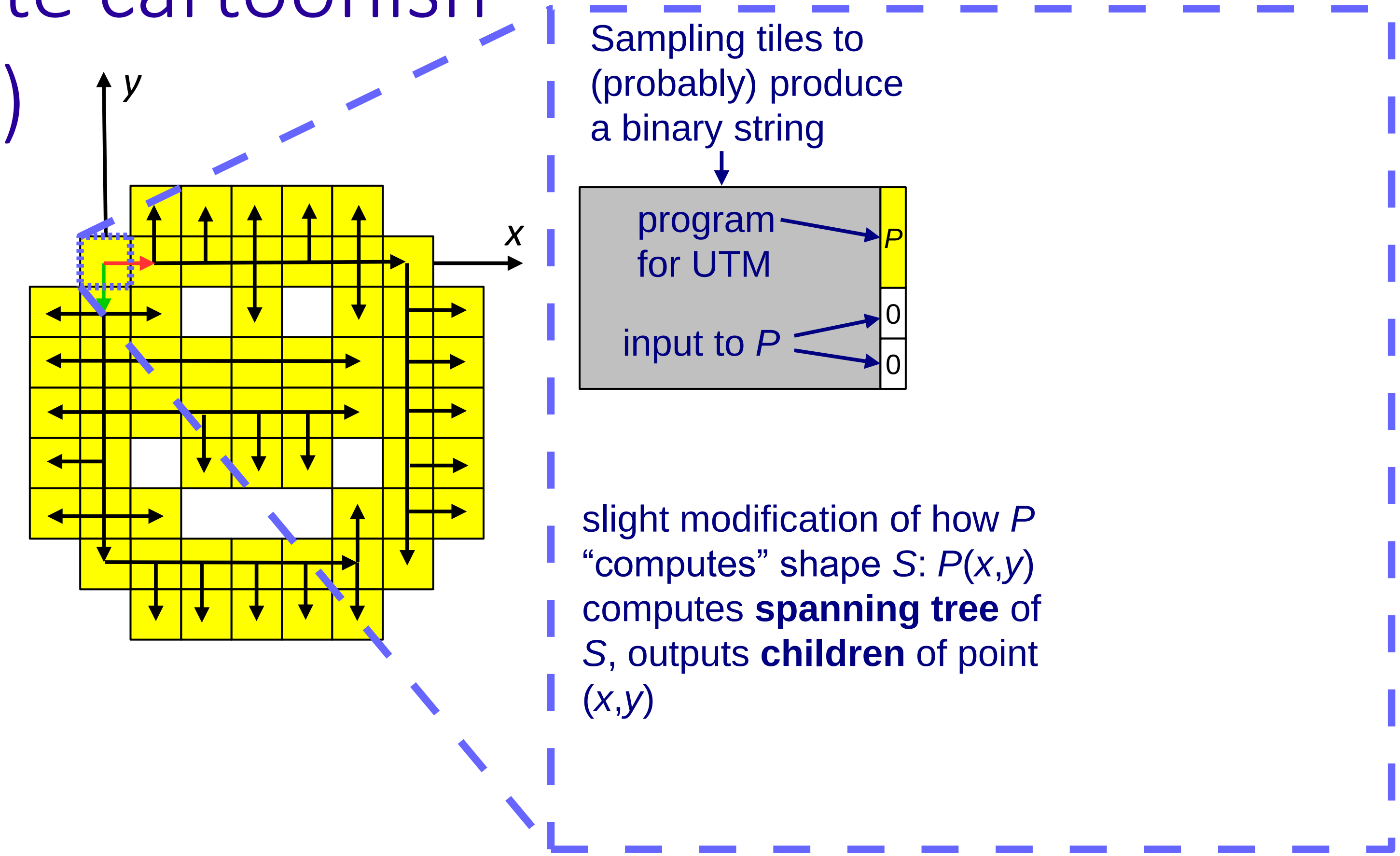

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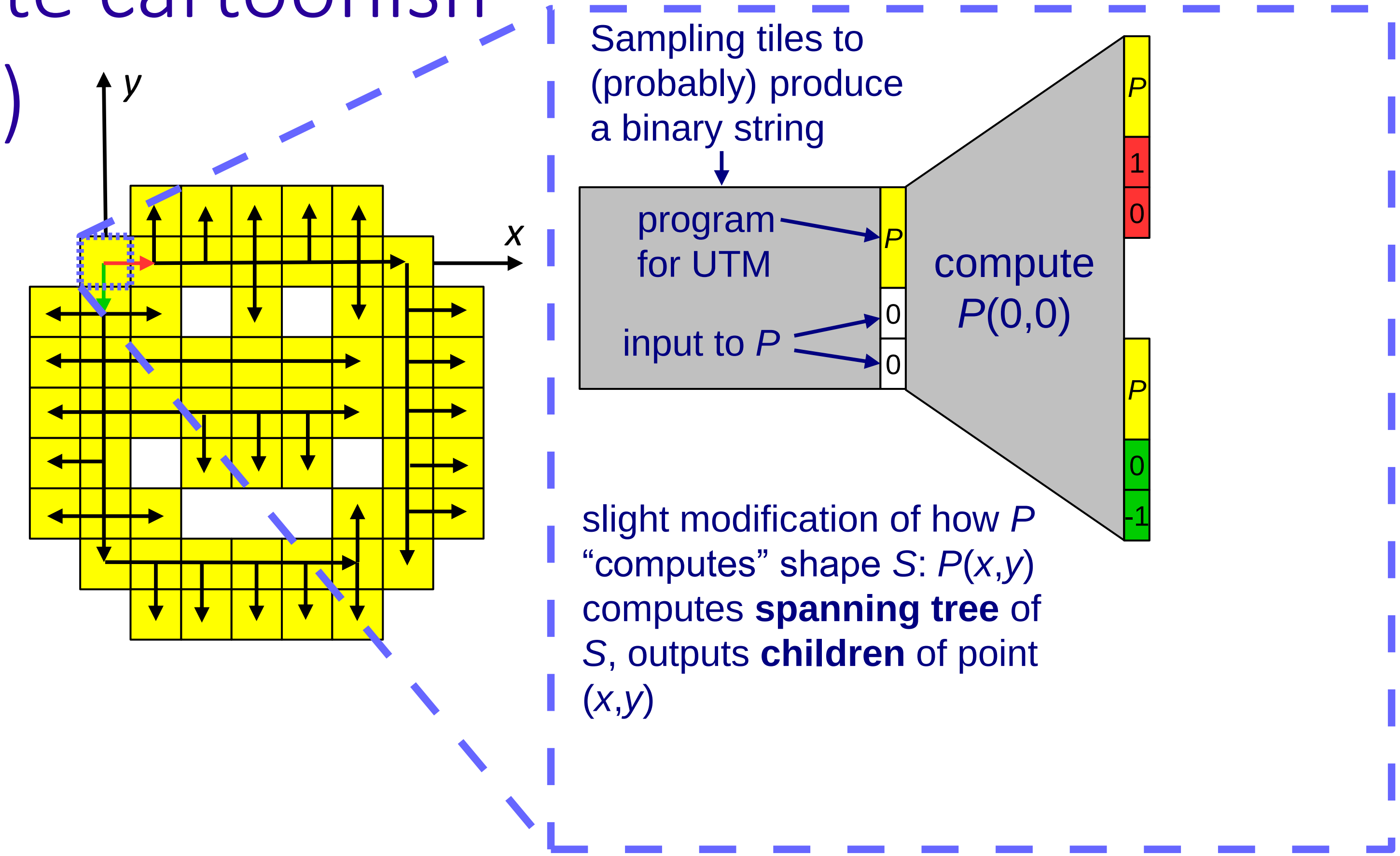

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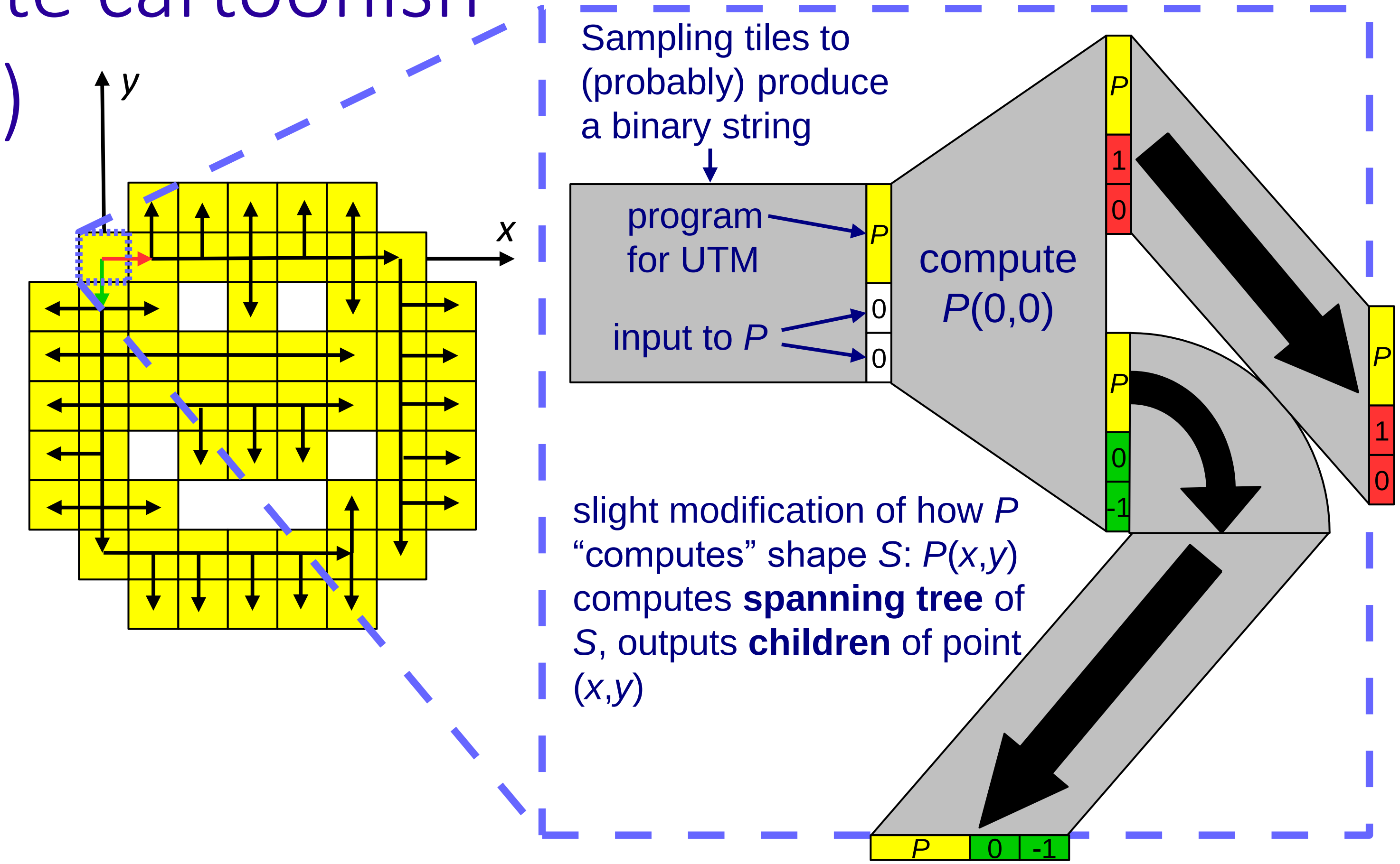

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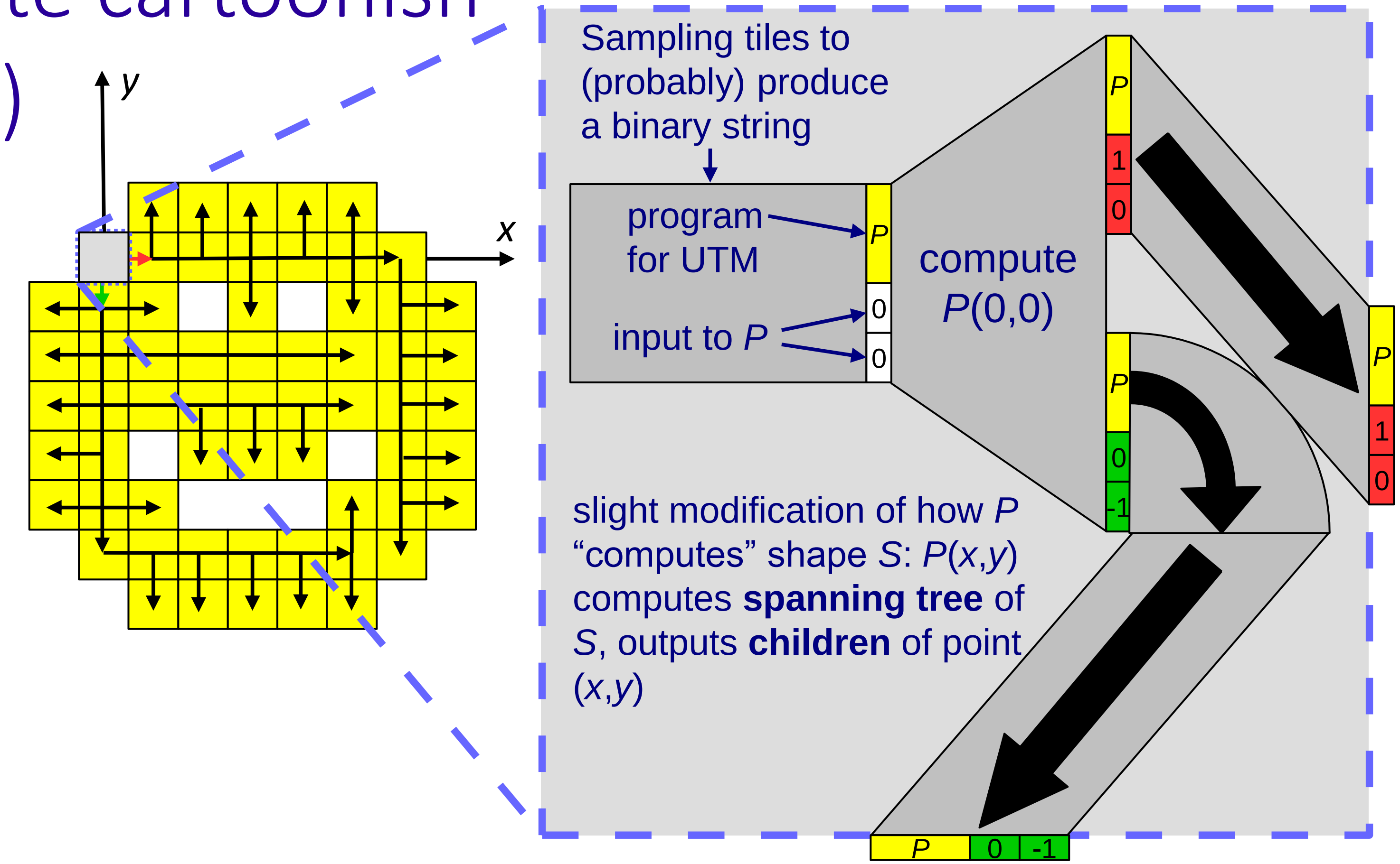

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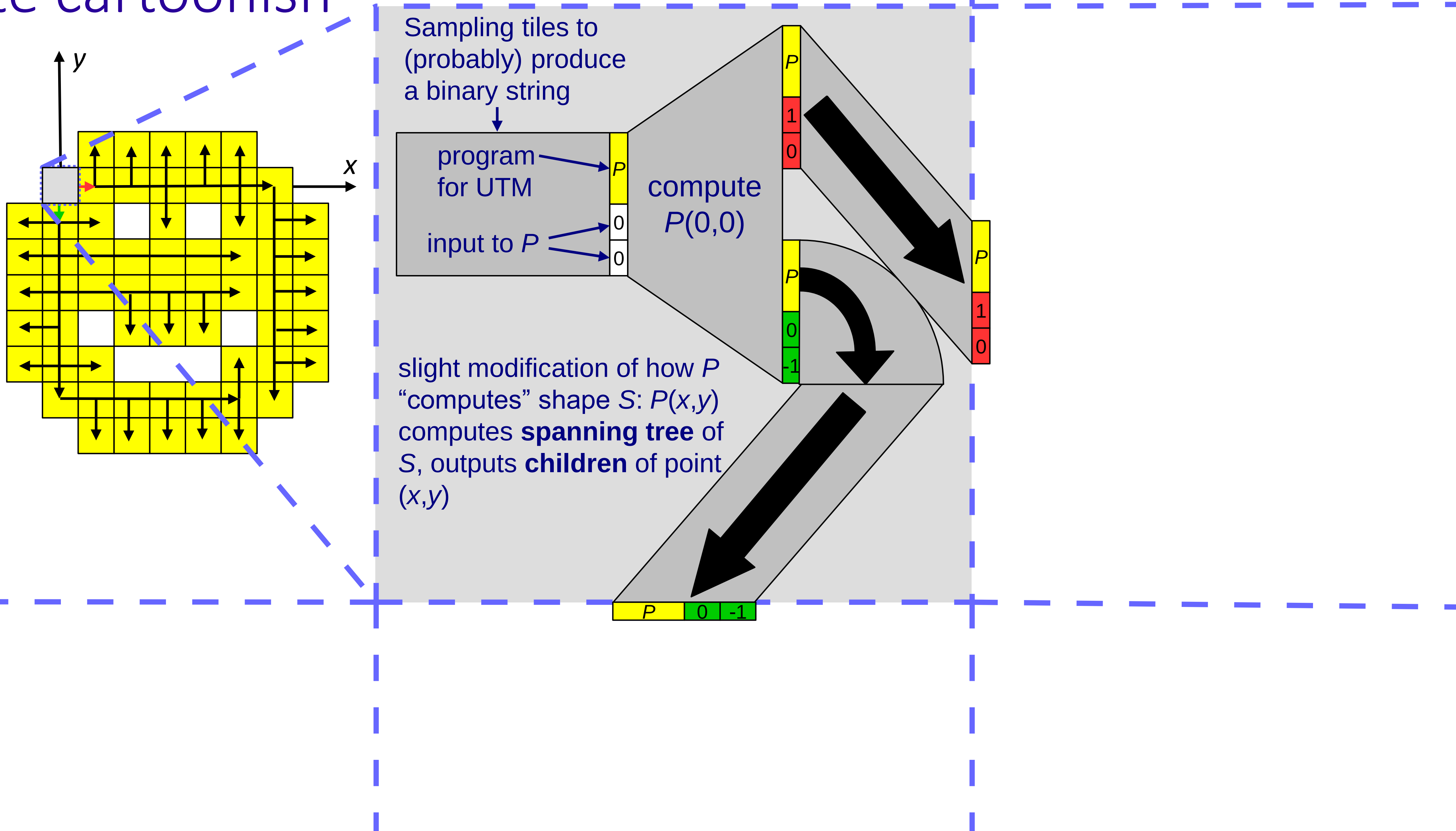

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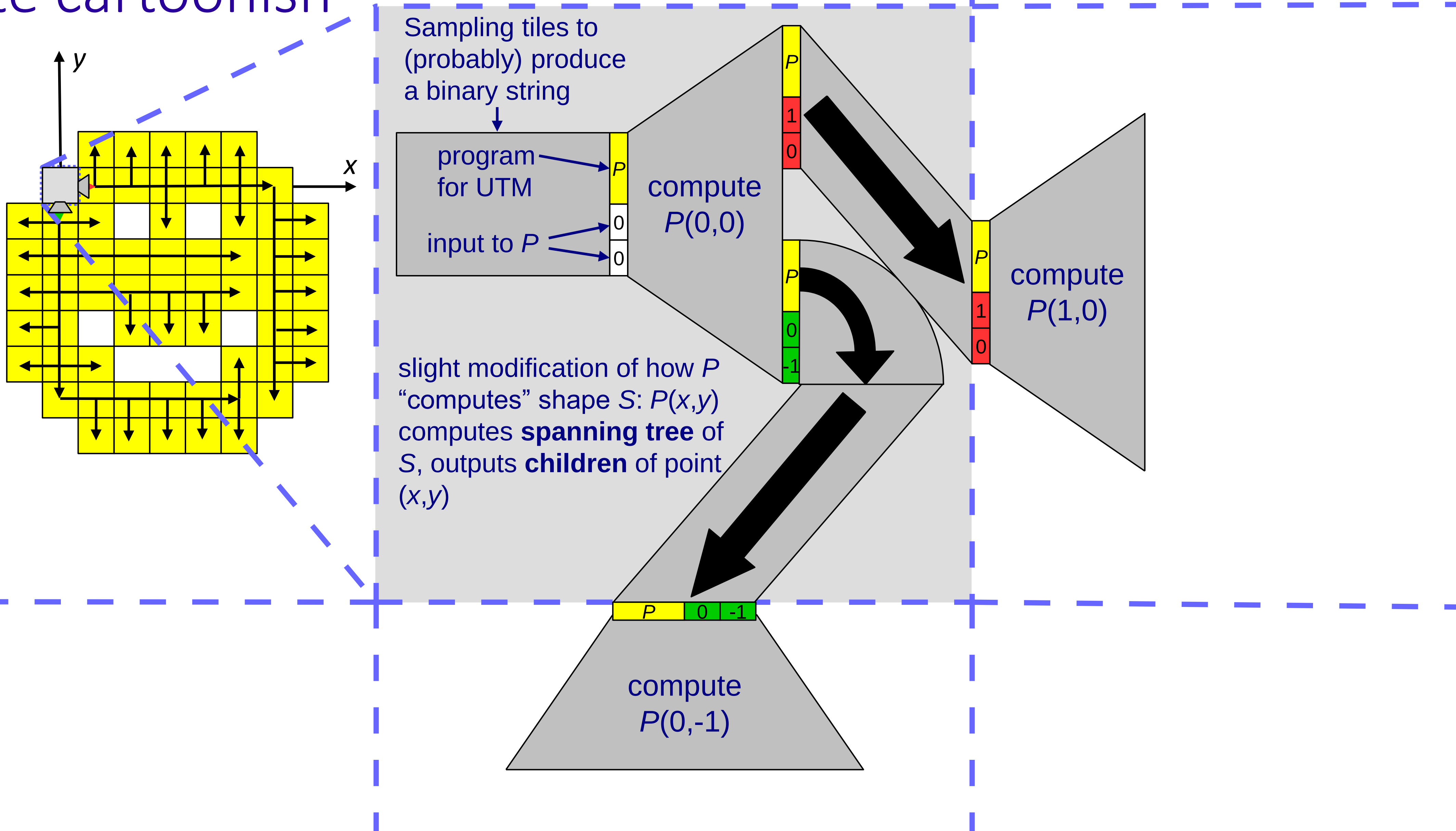

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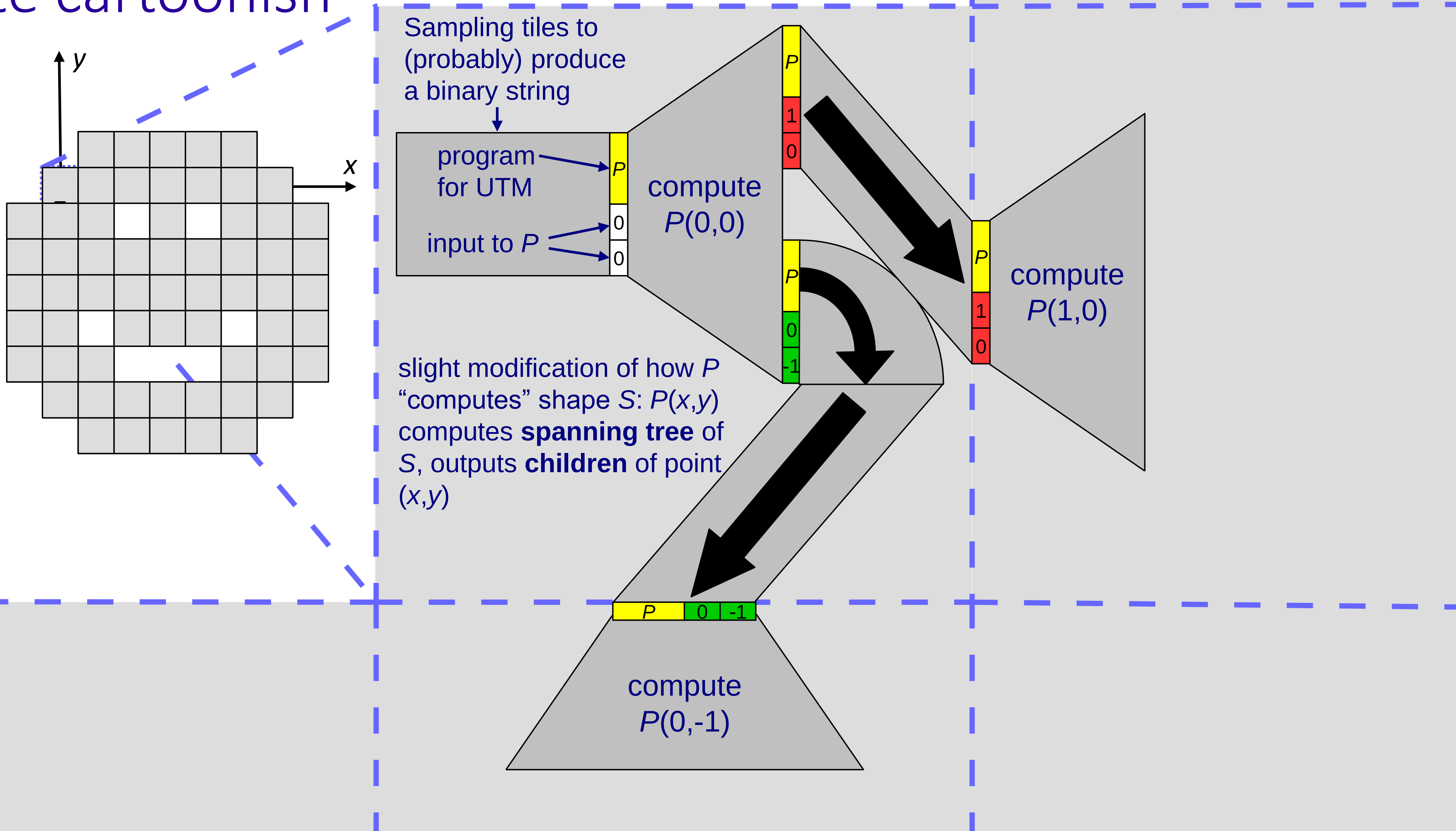

Universal self-assembling molecules

A **fixed** set of tile types can assemble *any* finite (scaled) shape (with high probability) by mixing them in the right concentrations.

[Doty, *Randomized self-assembly for exact shapes*, SICOMP 2010, FOCS 2009]

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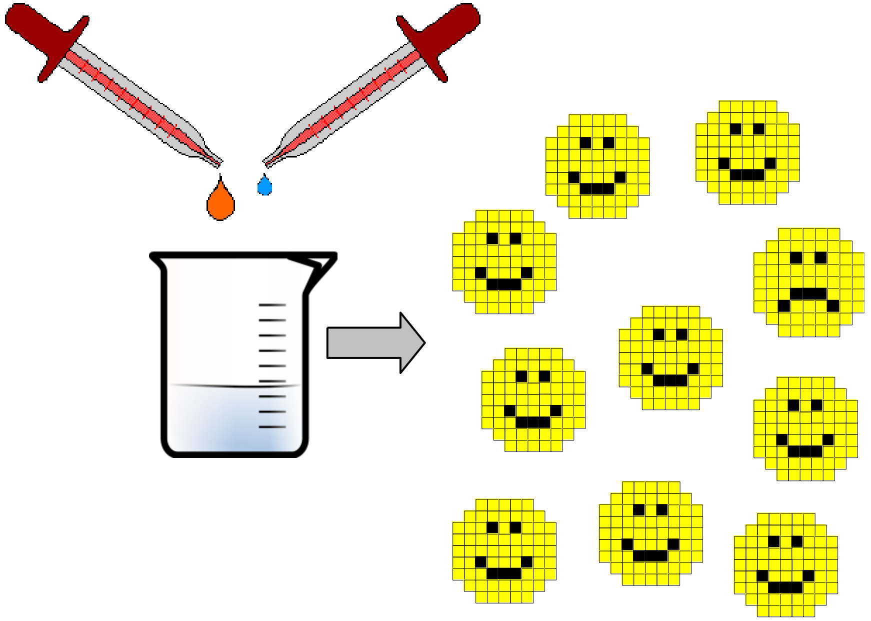

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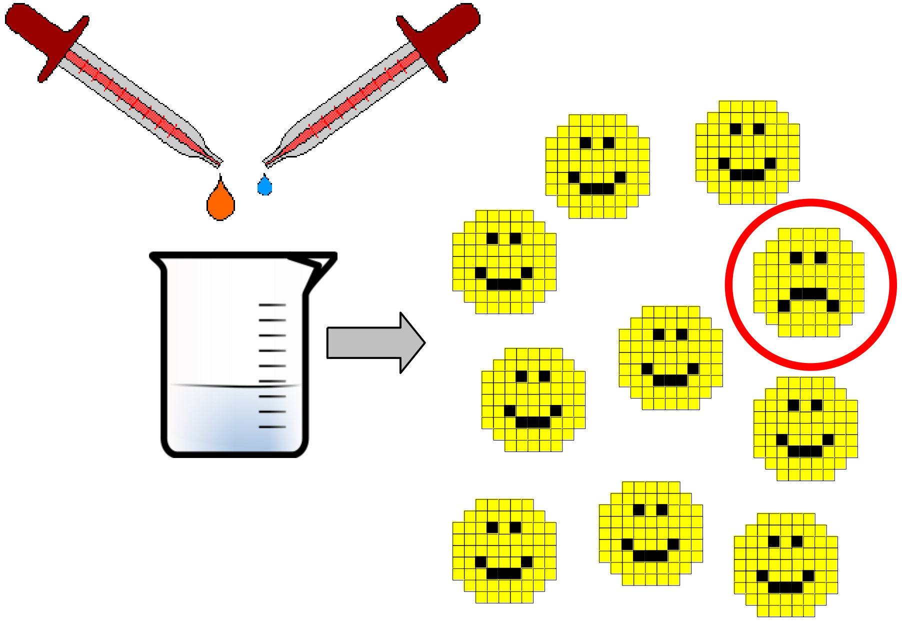

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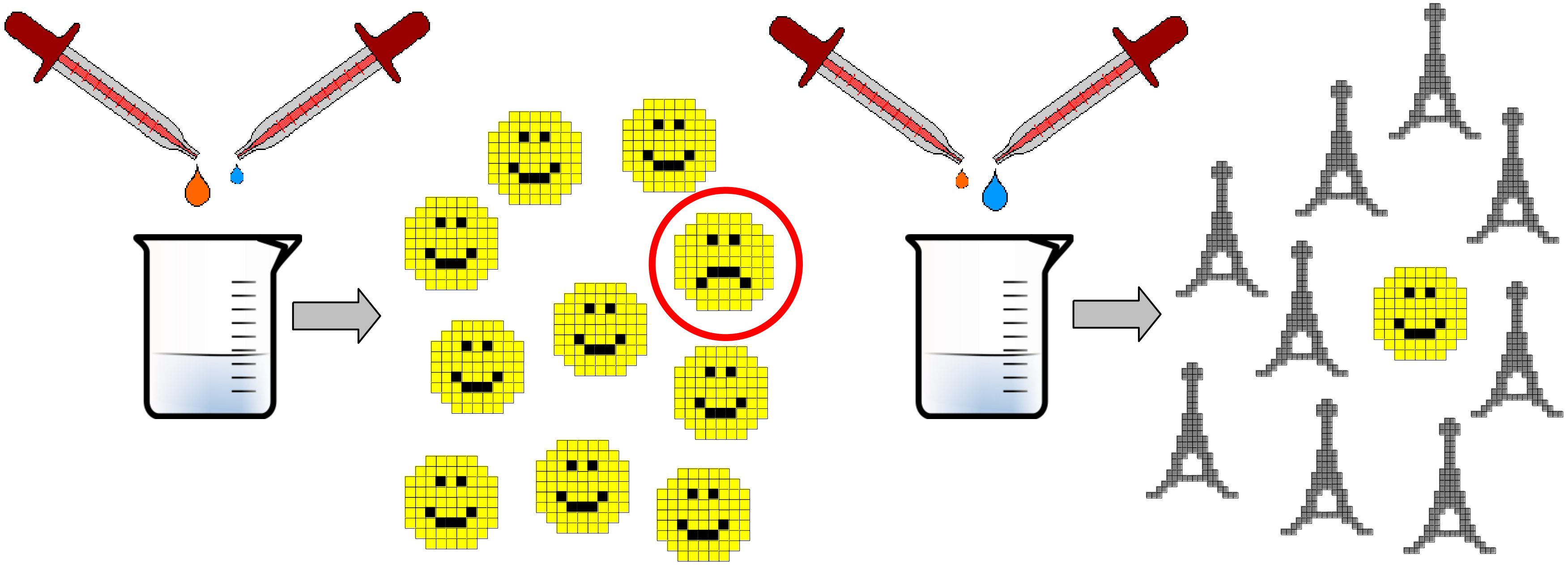

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Other plausible modifications of aTAM model that can reduce tile complexity

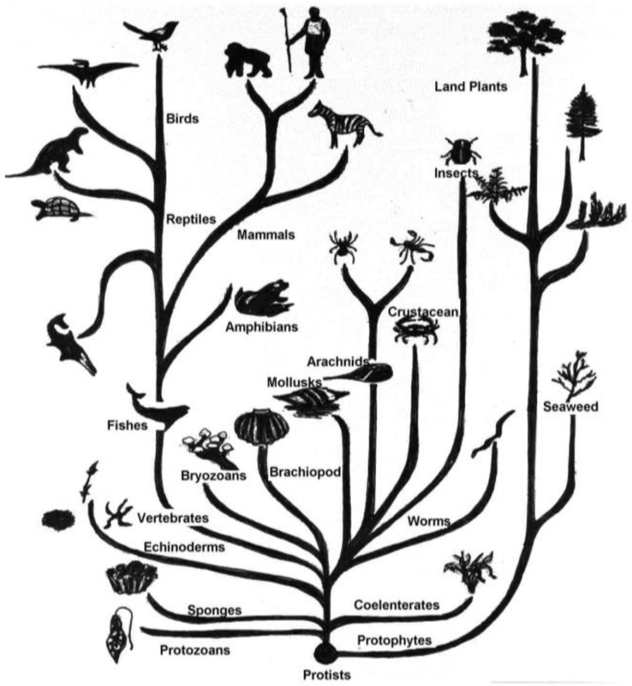
- staged self-assembly:
  - https://doi.org/10.1007/s11047-008-9073-0
- temperature programming:
  - https://dl.acm.org/doi/10.5555/1109557.1109620

The power of nondeterminism in self-assembly

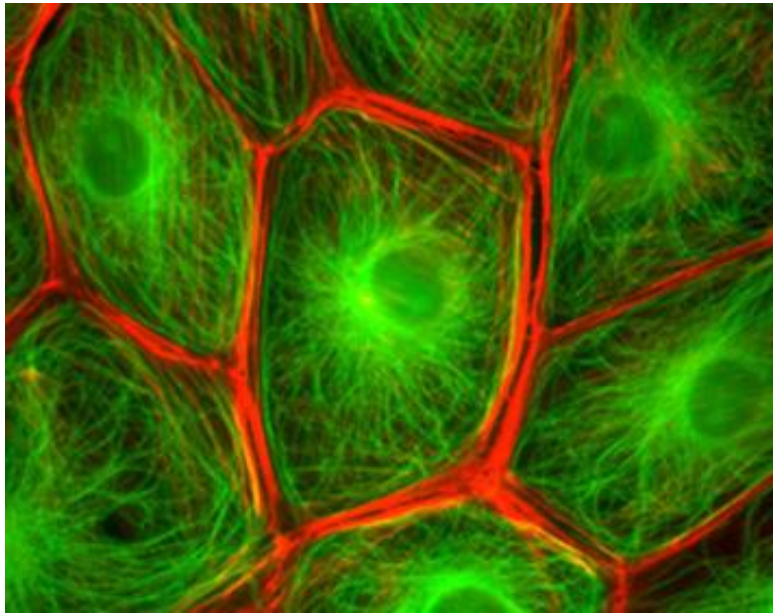
Can nondeterminism help to self-assemble shapes?

Nondeterminism in Biology

Genetic mutation



Cytoskeleton formation



Nondeterminism can allow complex structures to be created from a compact encoding.

Nondeterminism in Computer Science

Algorithm types:

Nondeterminism in Computer Science

Algorithm types:

Power

Deterministic: entire computation uniquely determined by input

Nondeterminism in Computer Science

Algorithm types:

Randomized: flips coins; realistic

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Algorithm types:

Nondeterministic: flips coins; magical

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Power

Nondeterminism in Computer Science

Algorithm types:

<u>Nondeterministic</u>:
flips coins; magical

<u>Randomized</u>:
flips coins; realistic

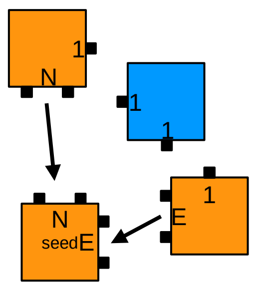
<u>Trivially nondeterministic (“pseudodeterministic”)</u>:
flips coins, but *final output* independent of flip results

<u>Deterministic</u>: entire computation uniquely determined by input

Power

Nondeterminism in Self-Assembly

Perhaps:



≥ 2 potential
binding sites

Nondeterminism in Self-Assembly

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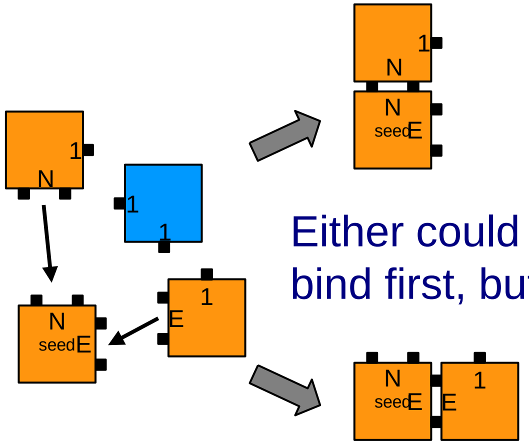

Either could bind first, but ...

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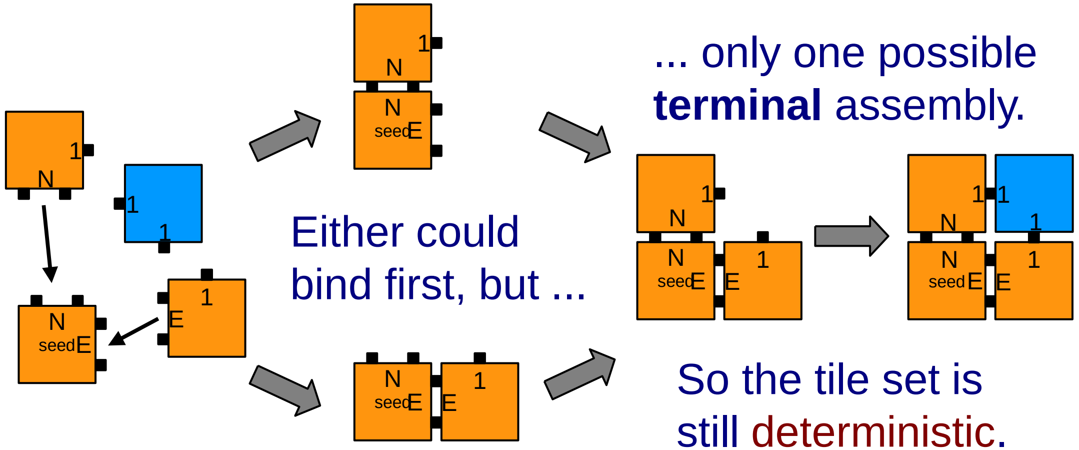

Either could bind first, but ...

... only one possible **terminal** assembly.

So the tile set is still deterministic.

Nondeterminism in Self-Assembly

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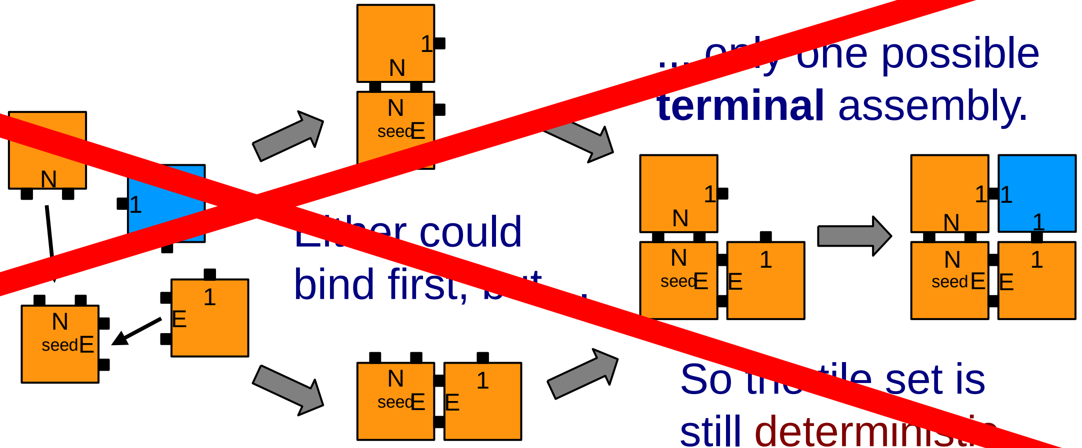

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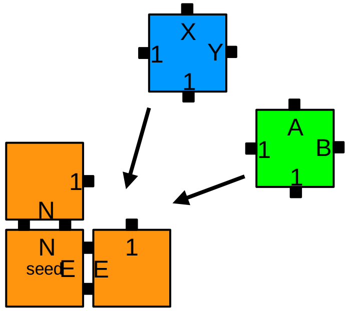
at a *single* binding site, ≥ 2 tile types attachable



If tile types compete ...

Nondeterminism in Self-Assembly

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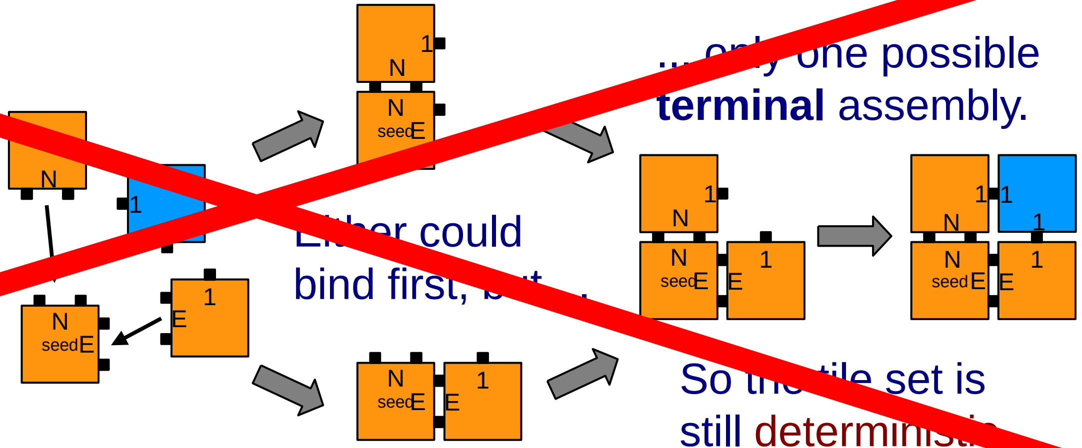

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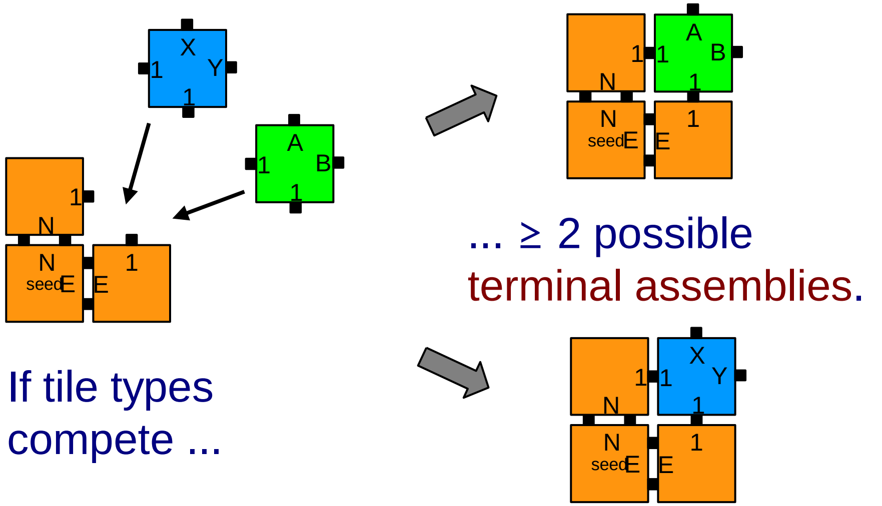

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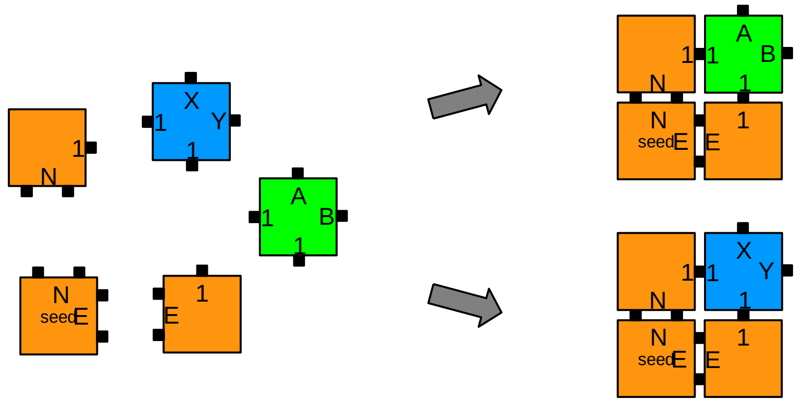
Nondeterminism in Self-Assembly

- A tile set is **deterministic** if it has only one terminal assembly (map of tile types to points).

Nondeterminism in Self-Assembly

- A tile set is **deterministic** if it has only one terminal assembly (map of tile types to points).
- This tile set has multiple terminal assemblies, *but* they all have the same shape.



- The tile set **self-assembles** a 2 x 2 square.

Power of Nondeterminism

Question: Let *S* be a finite shape self-assembled by some nondeterministic tile set. Does some deterministic tile set also self-assemble *S*?

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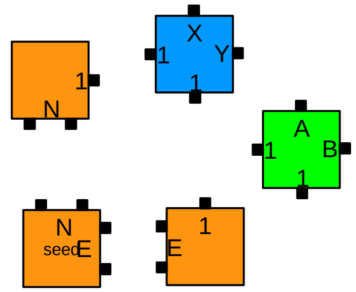

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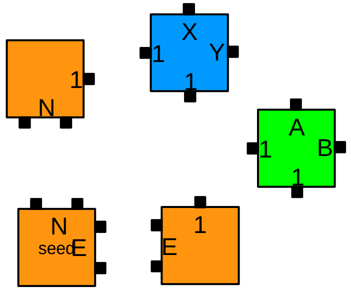
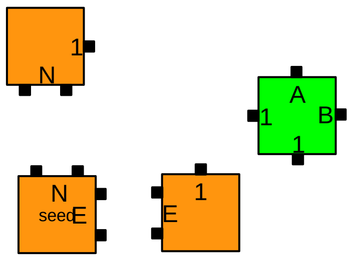


... to this deterministic tile set that self-assembles the same shape.



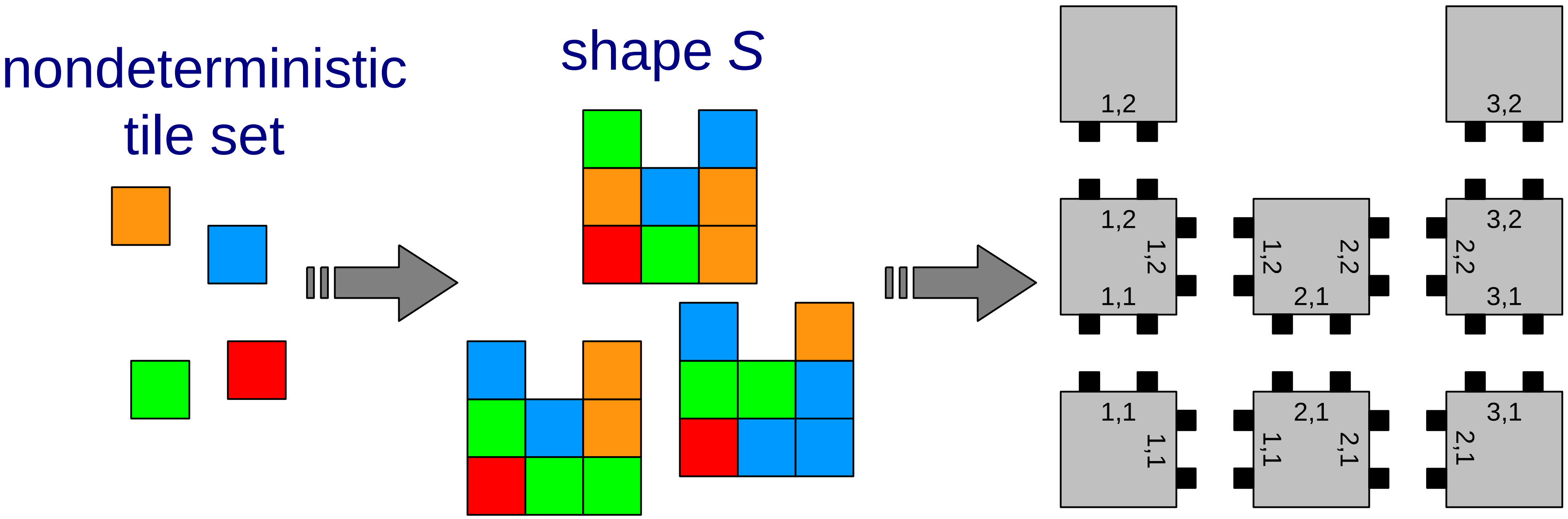
In general???

Power of Nondeterminism

Question: Let S be a finite shape self-assembled by some nondeterministic tile set. Does some deterministic tile set also self-assemble S?

Answer: Trivially yes.

deterministic tile set
(hard-coding S)



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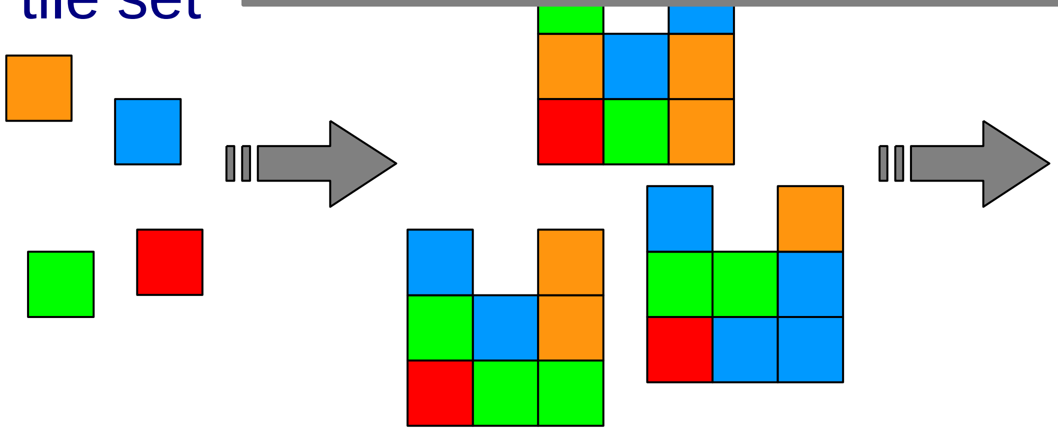
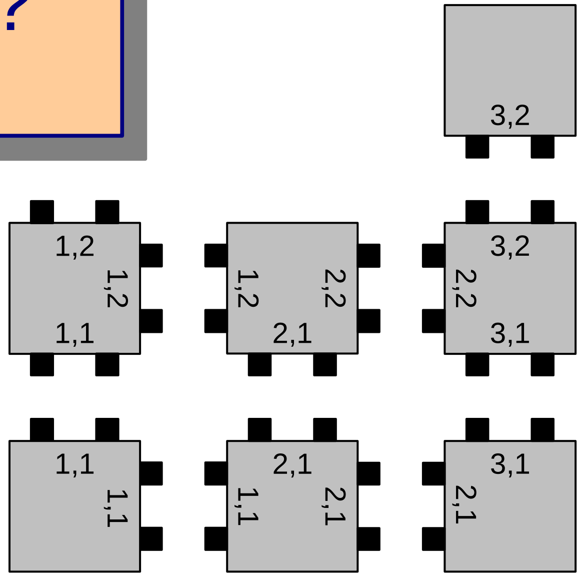
Is there **some** way that nondeterminism helps to self-assemble shapes?

nondetermin
tile set





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Remainder of talk

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Is *tile complexity* unaffected by nondeterminism?

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Optimization Problems

MINTILESET

Given: finite shape S

Find: size of smallest tile system that self-assembles S

Optimization Problems

MinTileSet

Given: finite shape S

Find: size of smallest tile system that self-assembles S

MinDetTileSet

Given: finite shape S

Find: size of smallest **deterministic** tile system that self-assembles S

Optimization Problems

MINTILESET

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MINDETTILESET

Given: finite shape S

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False statement: Nondeterminism does not affect tile complexity: for every nondeterministic tile set of size k that self-assembles a shape S, there is a deterministic tile set of size at most k that self-assembles S.

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for every nondeterministic tile set of size *k* that self-assembles a shape *S*, there is a deterministic tile set of size at most *k* that self-assembles *S*.

if true, would imply MinDetTileSet = MinTileSet

Main Result

- We show: MinTileSet is **NP**$^{\mathbf{NP}}$-complete.

  a.k.a., Σ_2^P

- MinDetTileSet is **NP**-complete. (Adleman, Cheng, Goel, Huang, Kempe, Moisset de Espanés, Rothemund, *STOC* 2002)

- **NP** ≠ **NP**$^{\mathbf{NP}}$ ⇒ MinTileSet ≠ MinDetTileSet

Nondeterminism in Algorithms and Self-Assembly

Algorithm that flips coins but always produces same output

- coin flips **useless**

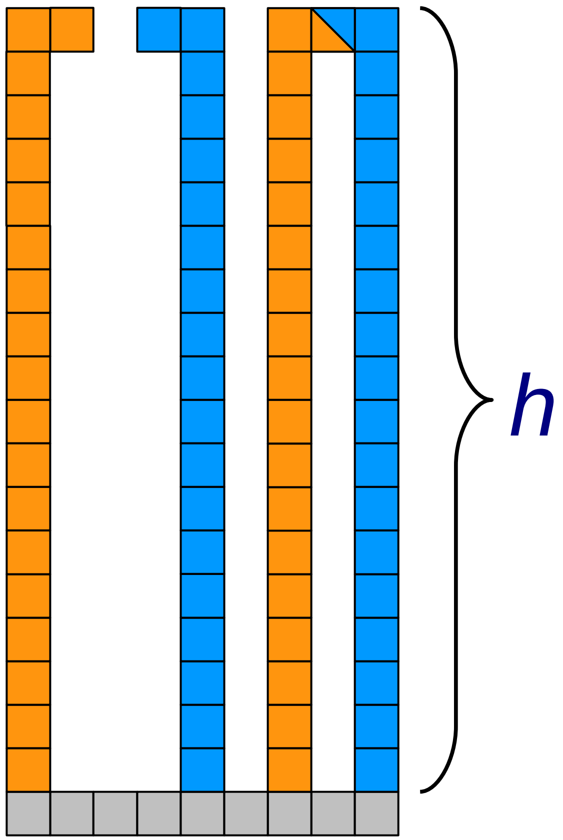
Tile set that flips coins but always produces same shape

- coin flips **useful**

But … finding smallest tile set is harder if it flips coins.

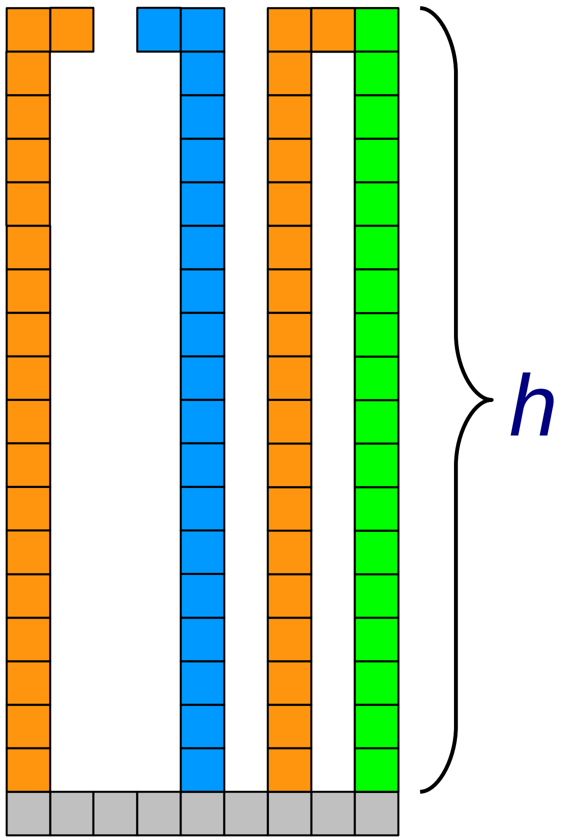
A Finite Shape for which Nondeterminism Affects Tile Complexity

- Smallest tile set: ≈ $2h$ tile types



A Finite Shape for which Nondeterminism Affects Tile Complexity

- Smallest tile set: ≈ $2h$ tile types
- Smallest *deterministic* tile set: ≈ $3h$ tile types

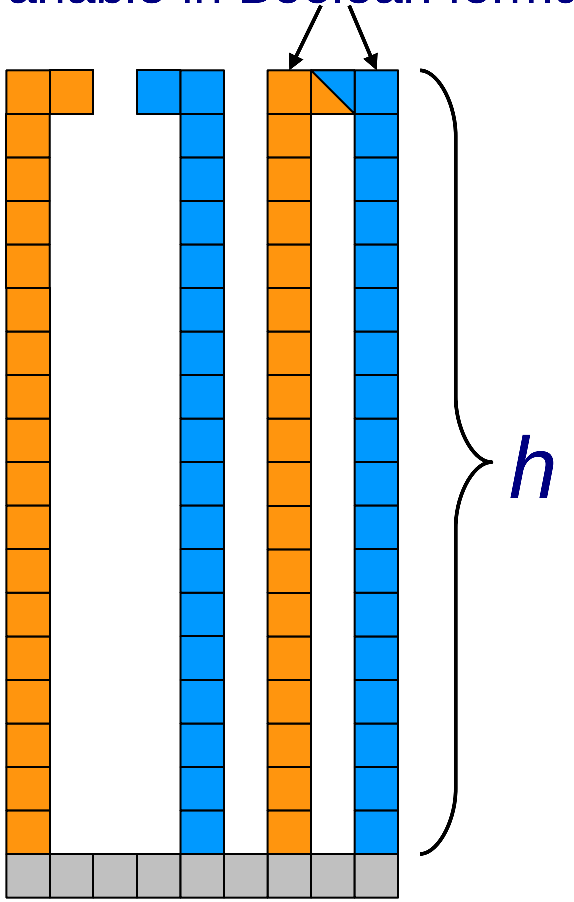


A Finite Shape for which Nondeterminism Affects Tile Complexity

in **NP**$^{\mathbf{NP}}$-hardness reduction, compete to assign bits to variable in Boolean formula

- Smallest tile set: ≈ 2*h* tile types

- Smallest *deterministic* tile set: ≈ 3*h* tile types



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- Given Φ, construct shape S and integer c such that $(\exists x)(\forall y)\neg\Phi(x,y)$ holds if and only if some tile set of size at most c self-assembles S.

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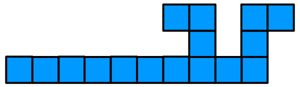

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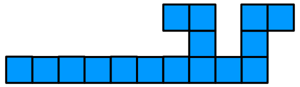

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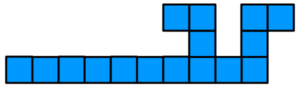

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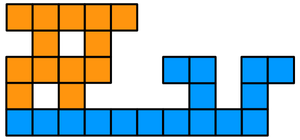

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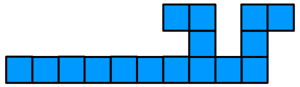

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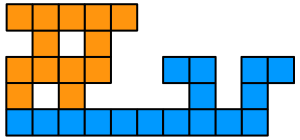

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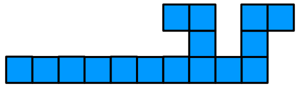

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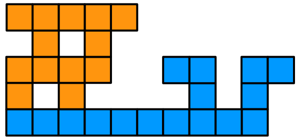

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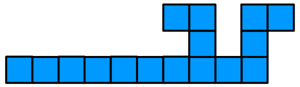

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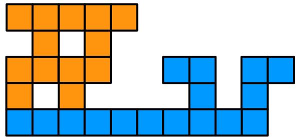

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  - Otherwise, tiles from *T* cannot be altered to assemble *S*.
  - "Since $\Upsilon \subseteq S$," every tile set that assembles *S* contains *T*, so if tiles from *T* cannot be altered to assemble *S* then additional tiles are needed; i.e., *S* requires more than $c = |T|$ tile types.

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C_3	SF	SF	ST	ST
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C_1	UF	UF	ST	ST
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→

highlighting when C_j goes from unsatisfied (U) to satisfied (S)

C_3	USF	SSF	SST	SST
C_2	UUF	UUF	UUT	UST
C_1	UUF	UUF	UST	SST
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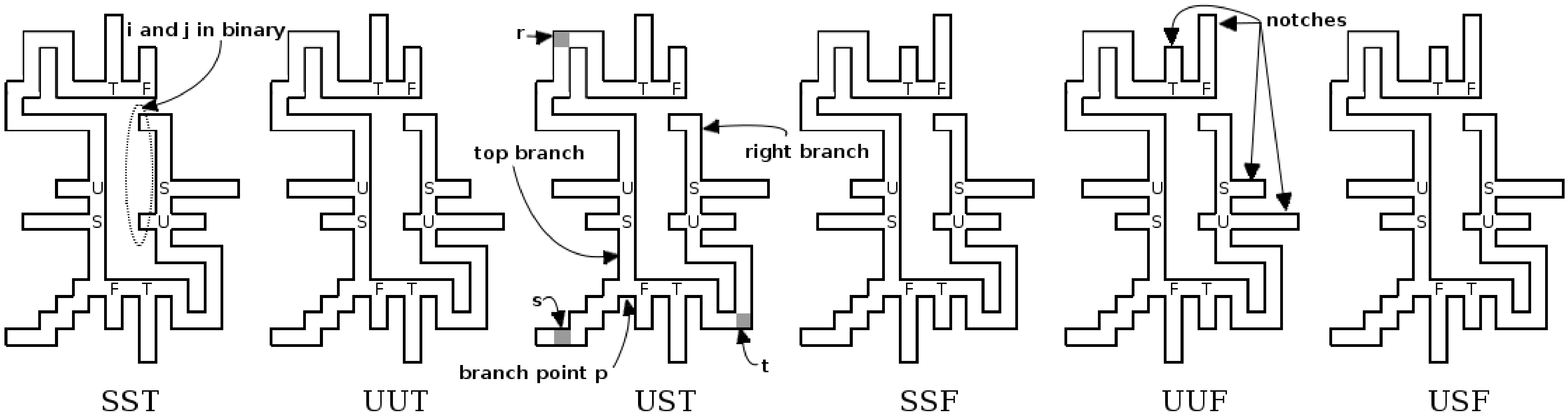
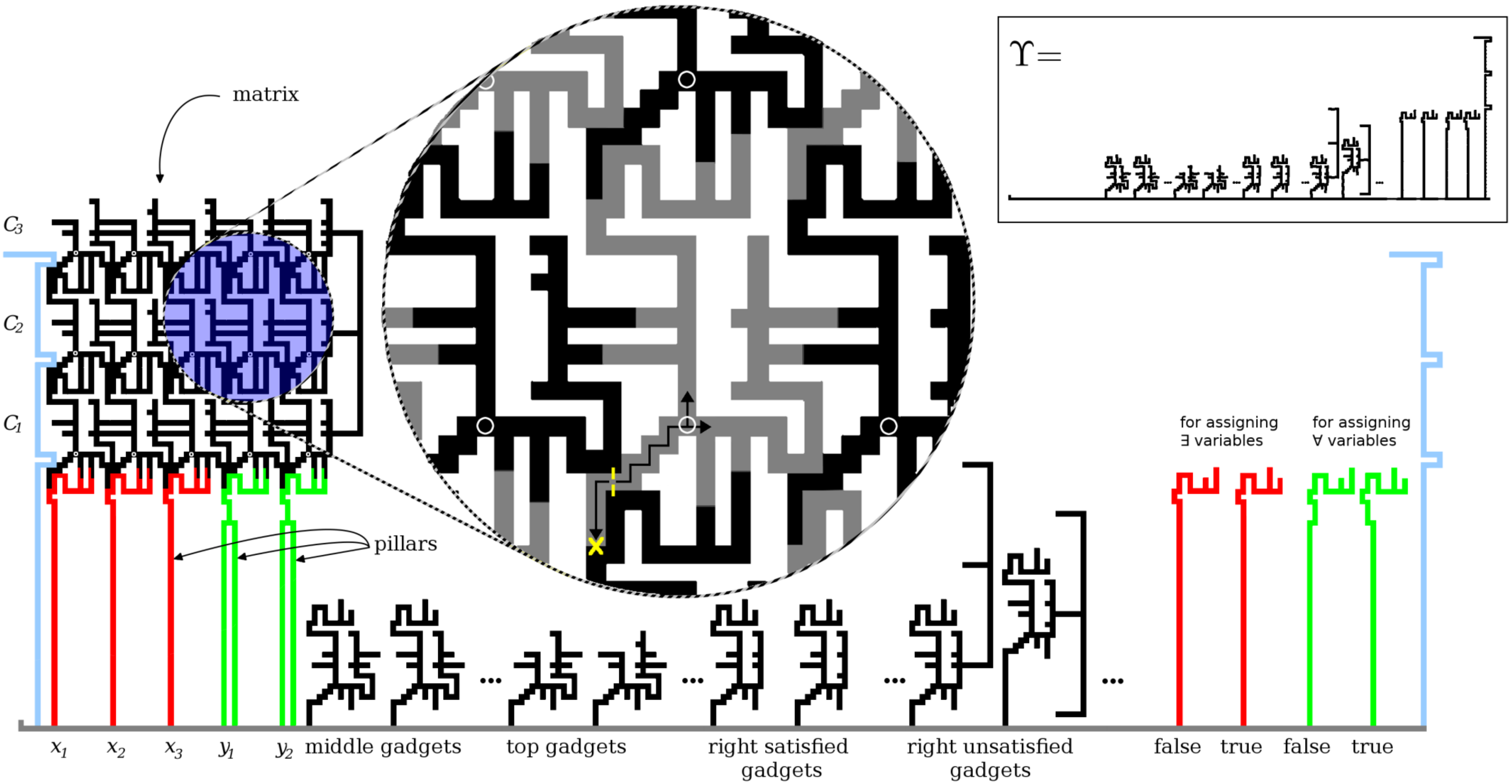
Gadgets (Adleman et al. 2002)



For each variable w_i and clause C_j, value of w_i = T/F and

SS_{ij} – C_j satisfied by a previous variable (w_k for $k < i$)
US_{ij} – C_j unsatisfied by previous variables but is satisfied by w_i
UU_{ij} – C_j unsatisfied by previous variables and by w_i

Shape S



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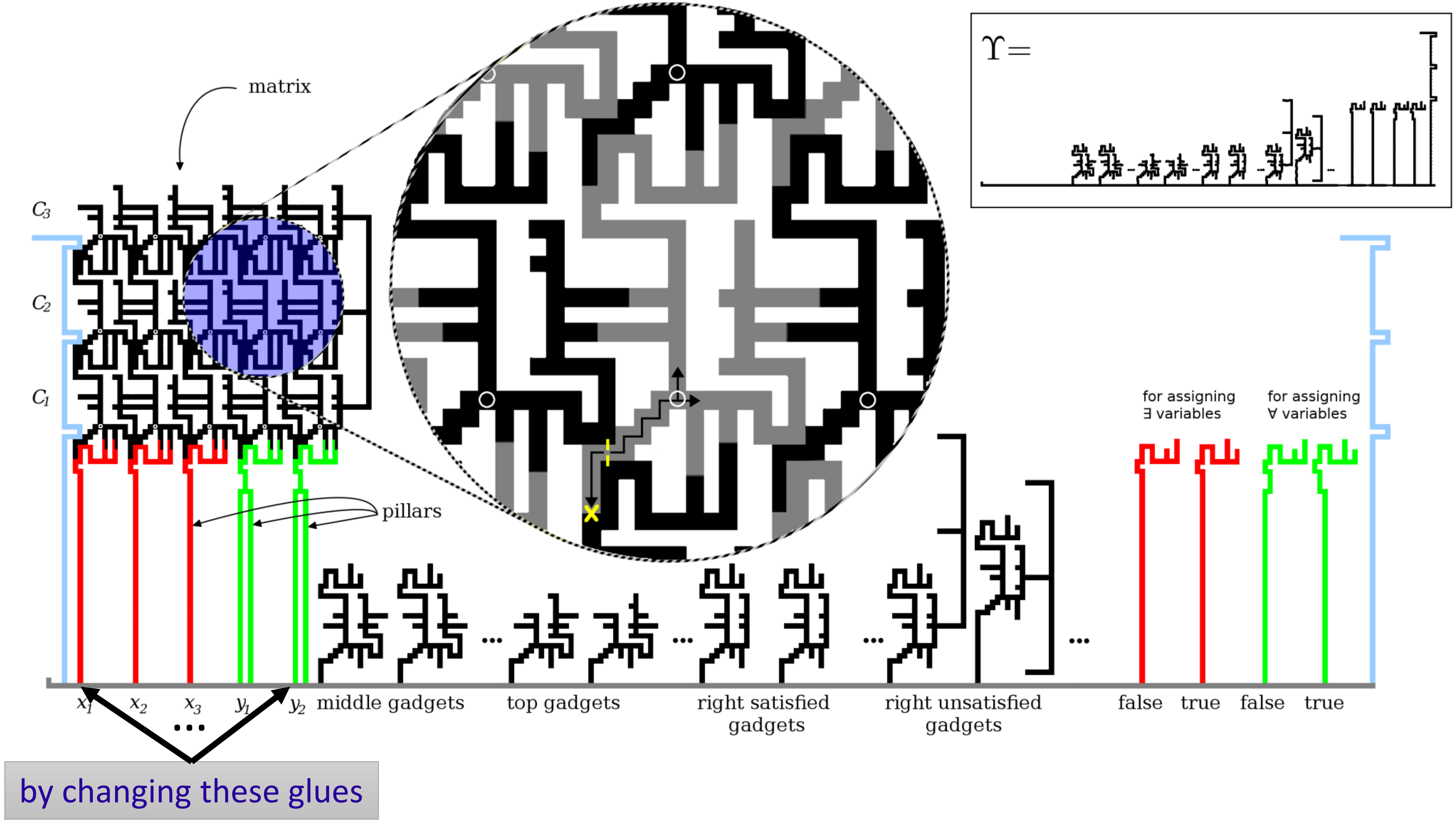

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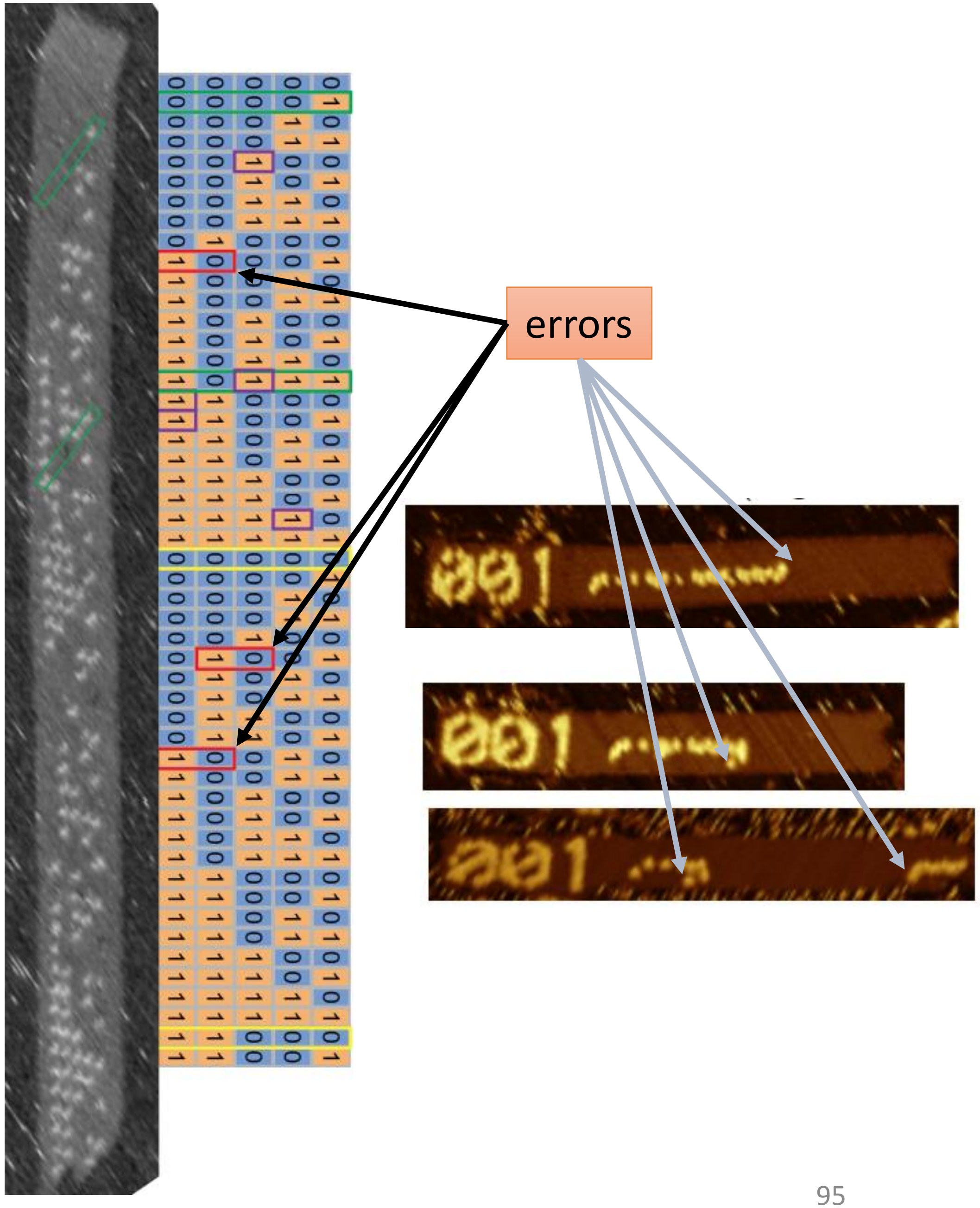

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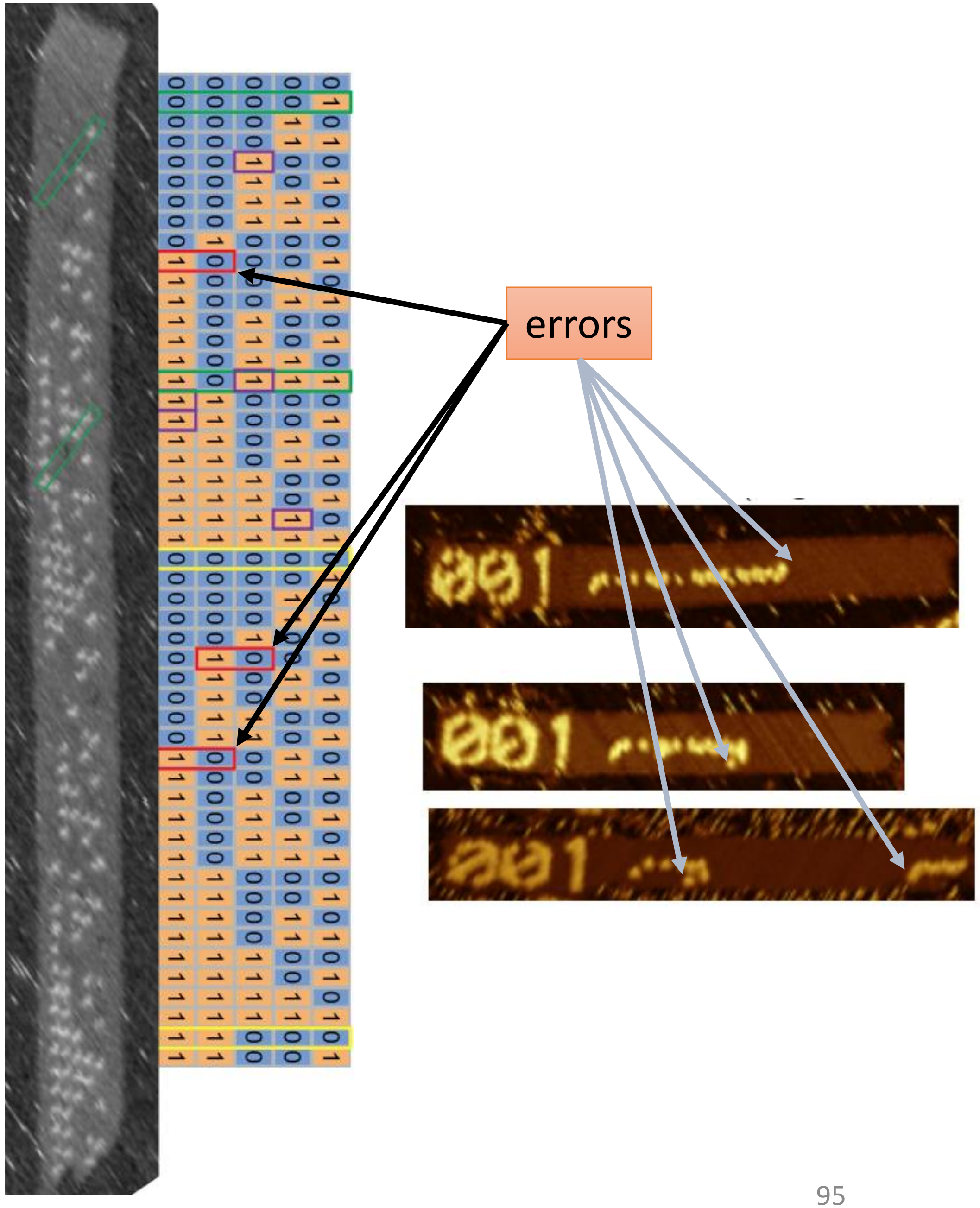

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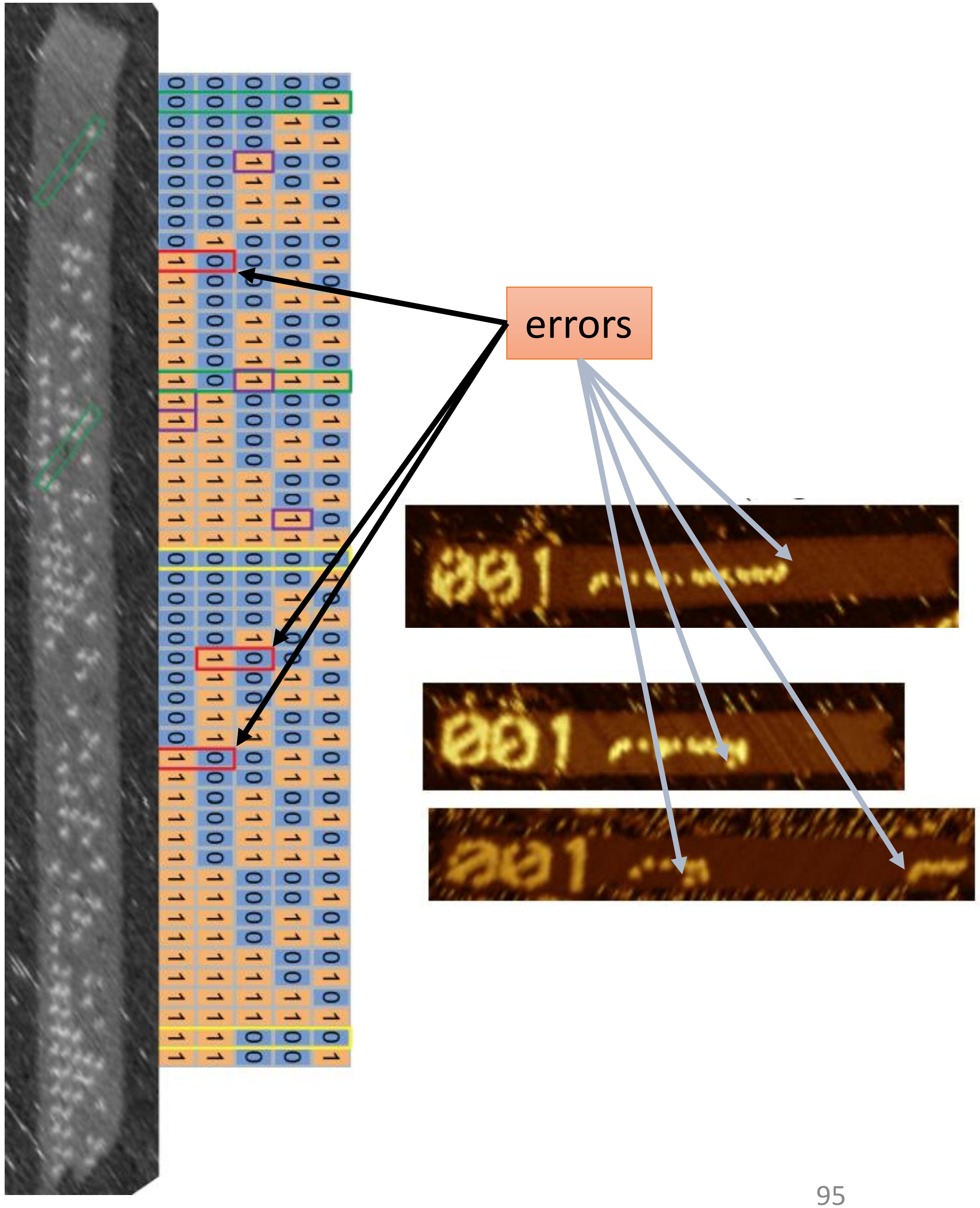
  - tiles can detach
  - tiles can bind with strength 1



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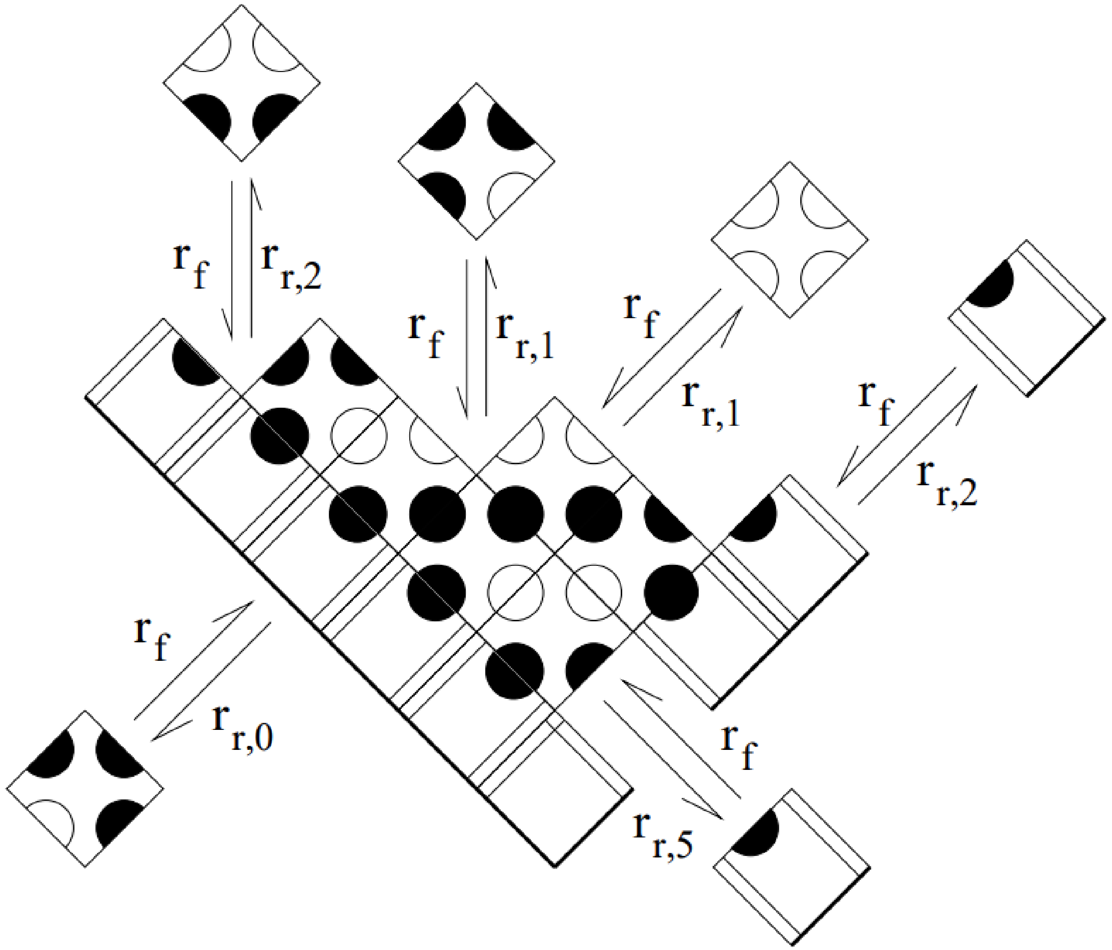

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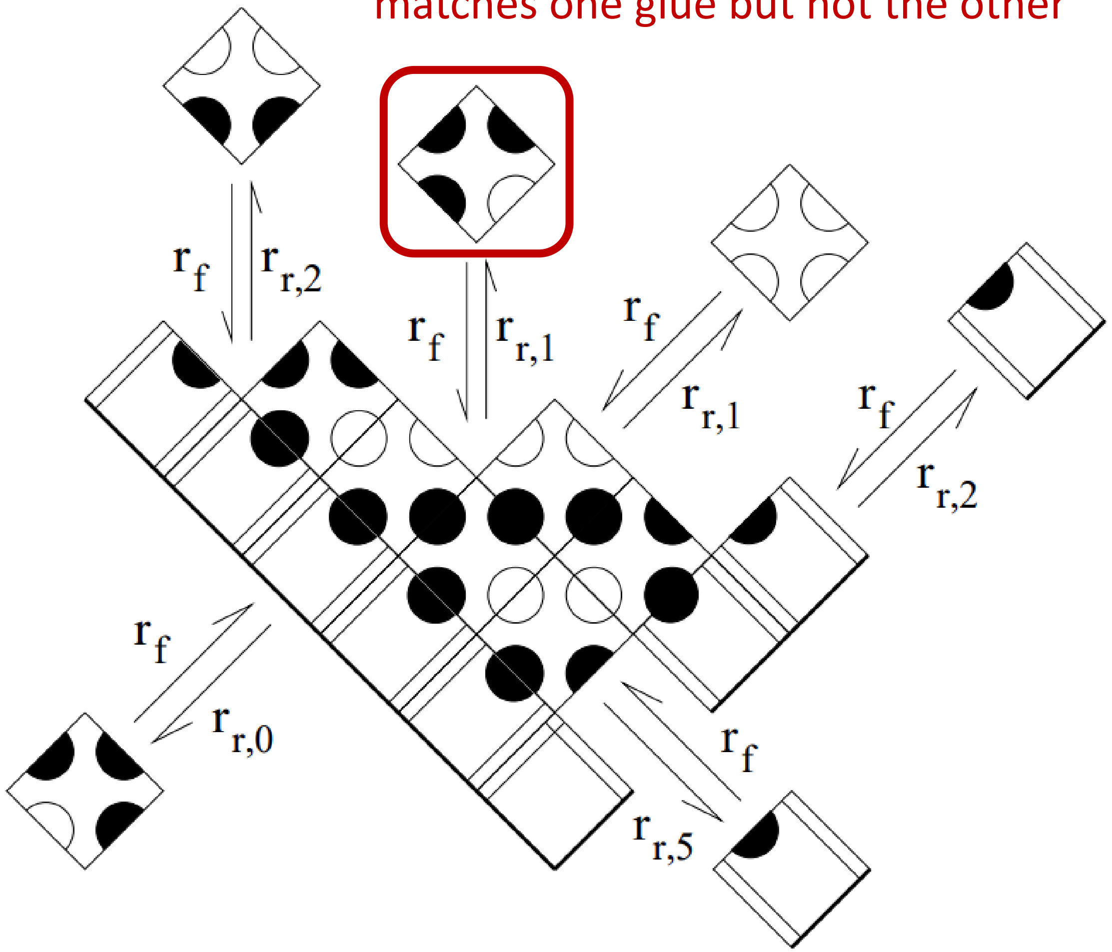

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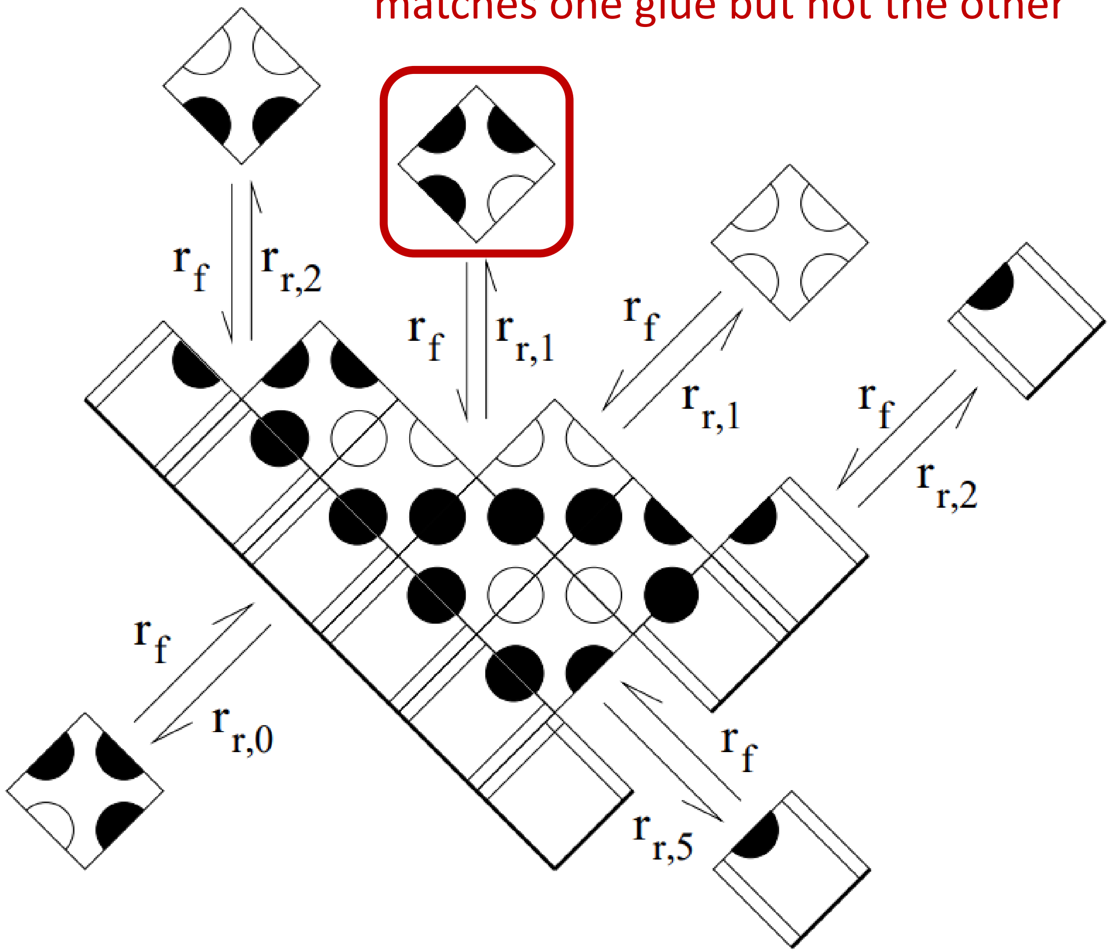

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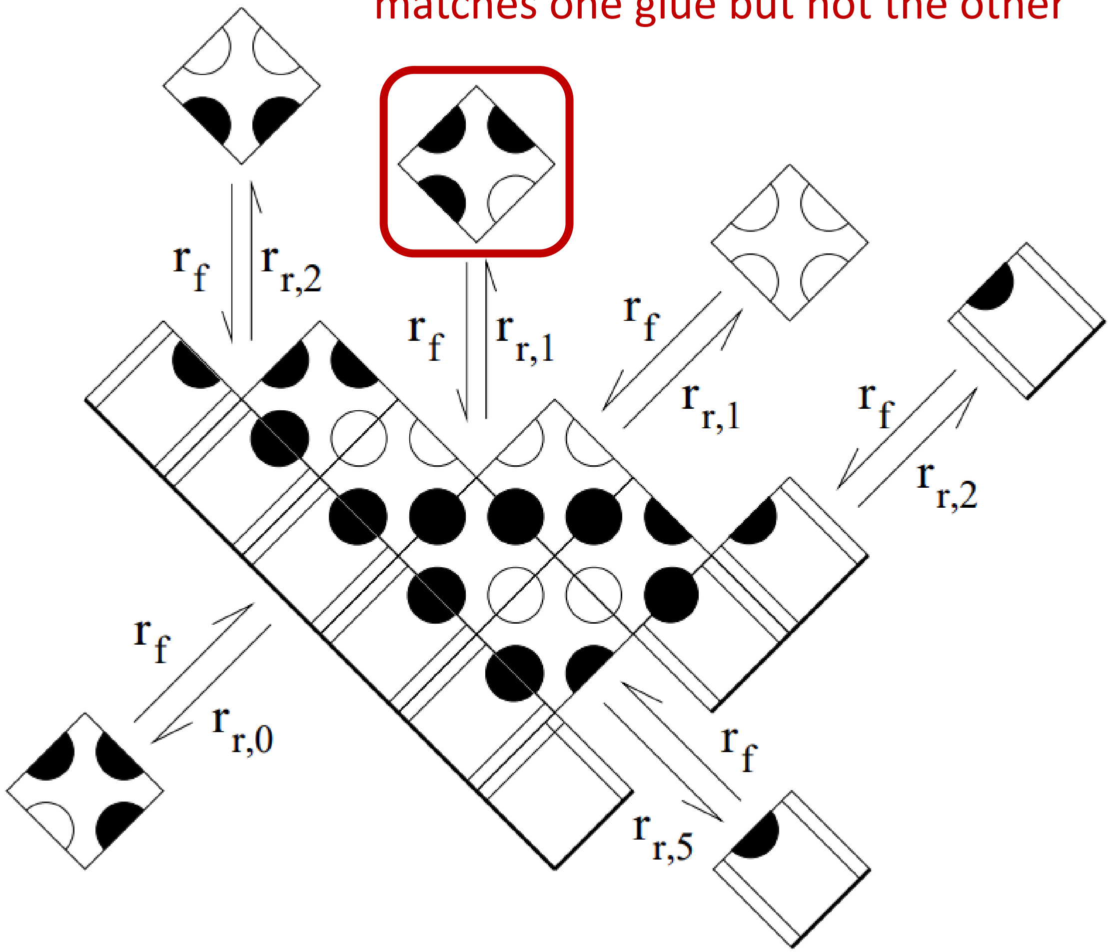

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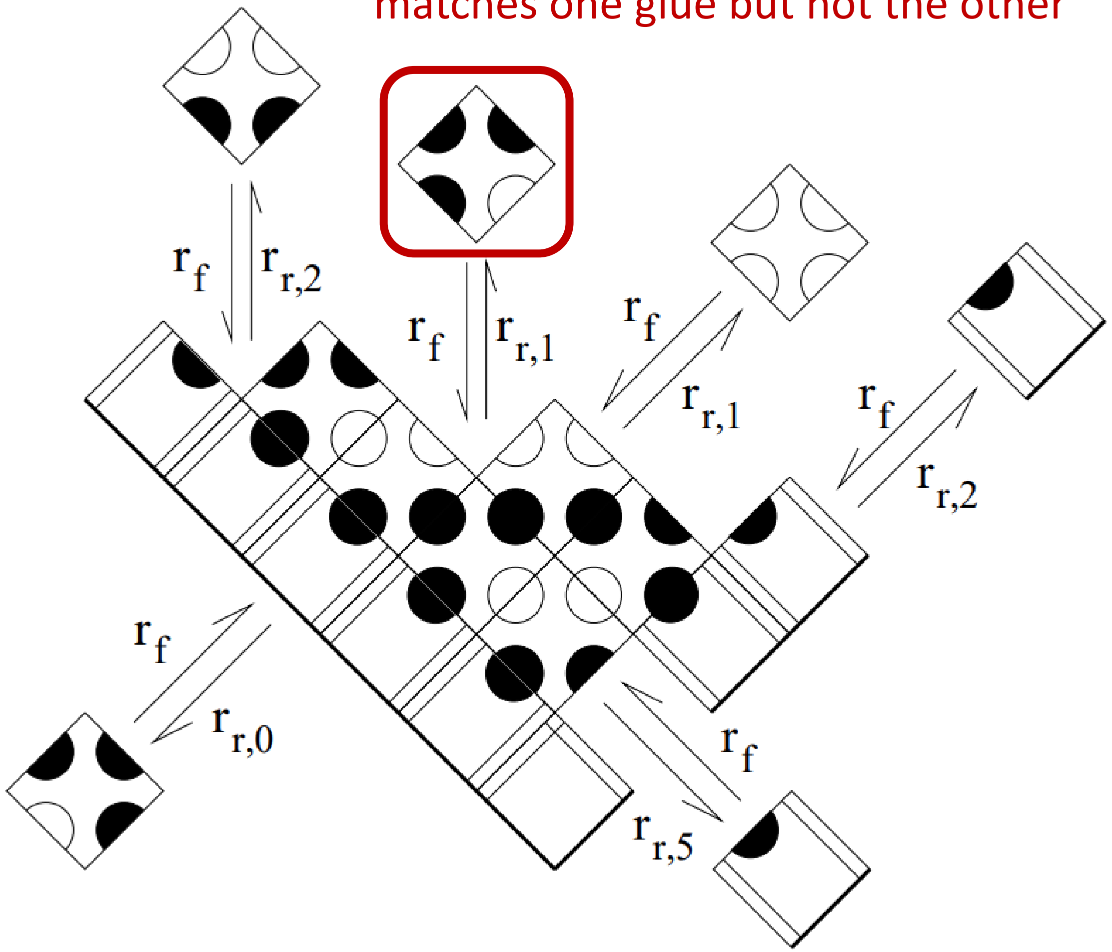

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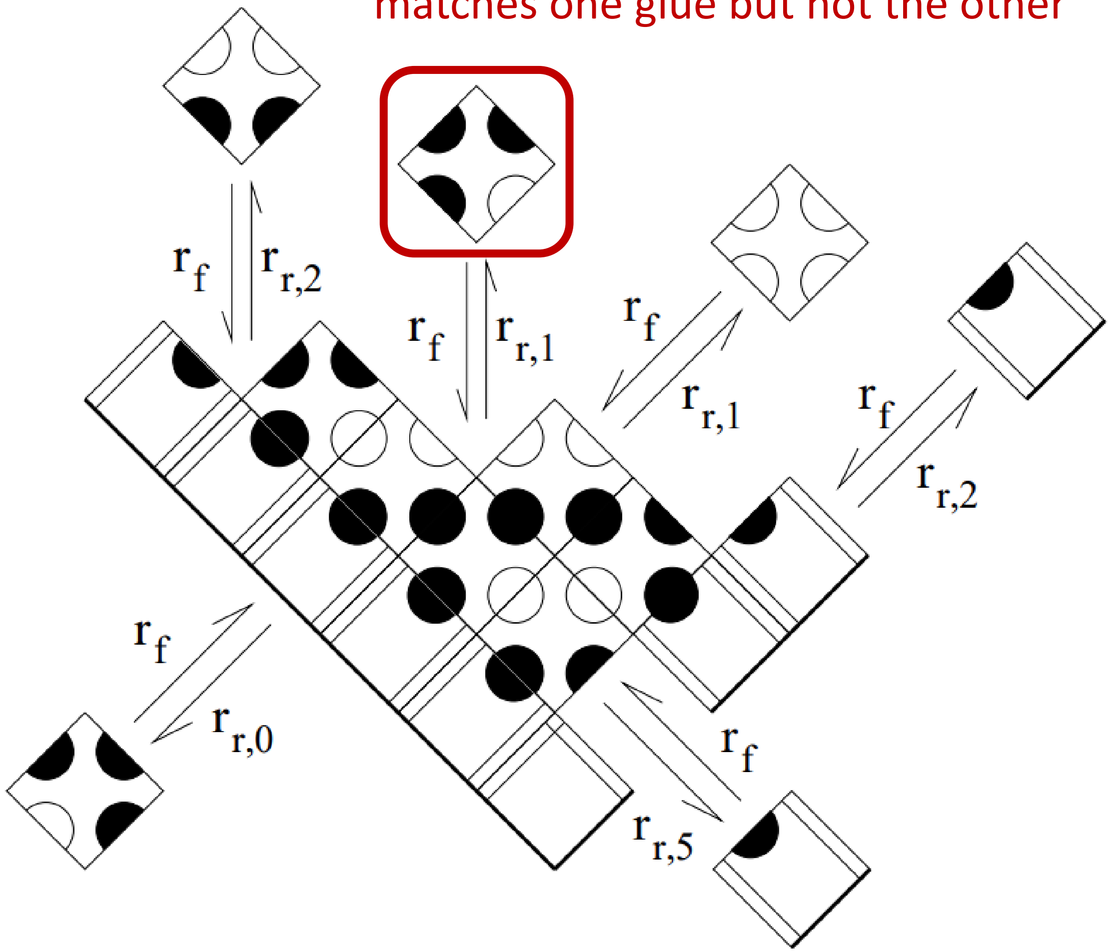

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- Take home message: tiles bound with fewer glues (potential errors) fall off faster, but could get locked in by subsequent neighboring attachment

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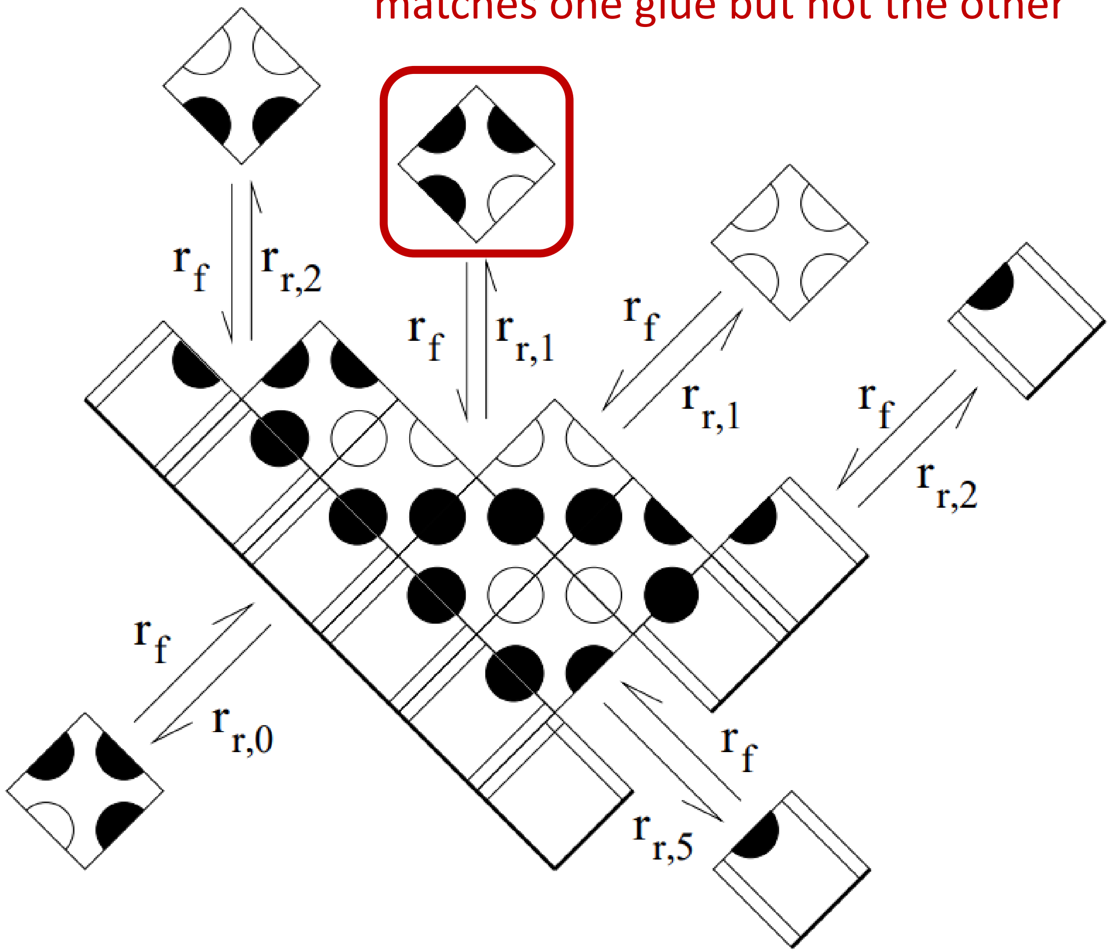

kTAM simulators

- ISU TAS (developed by Matt Patitz) also does kTAM simulation:
  - http://self-assembly.net/wiki/index.php?title=ISU_TAS
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- xgrow (developed by Erik Winfree)
  - https://www.dna.caltech.edu/Xgrow/
  - older and a bit less intuitive

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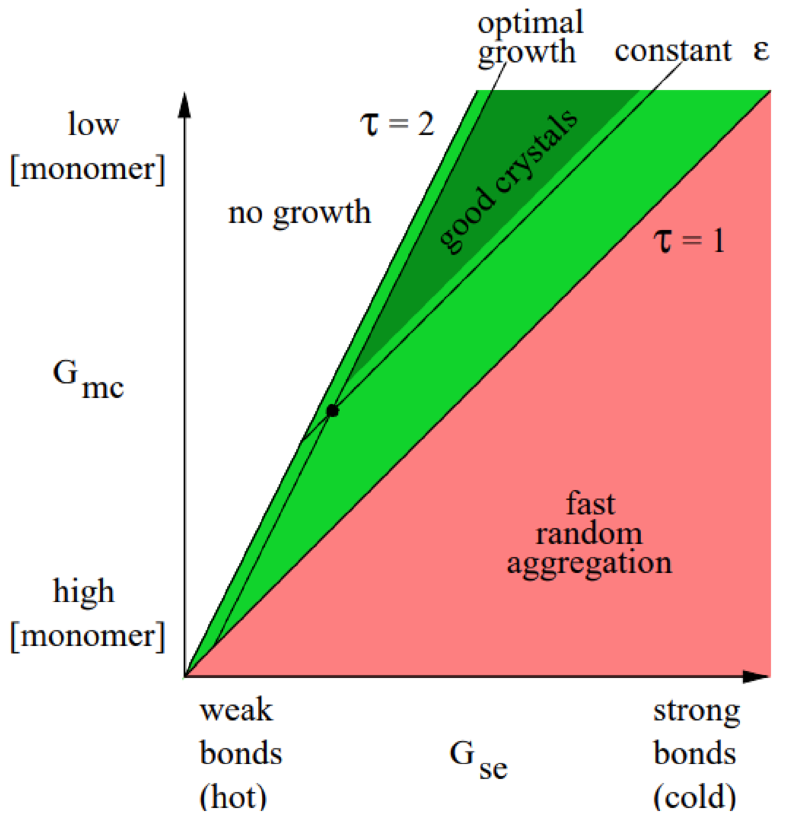

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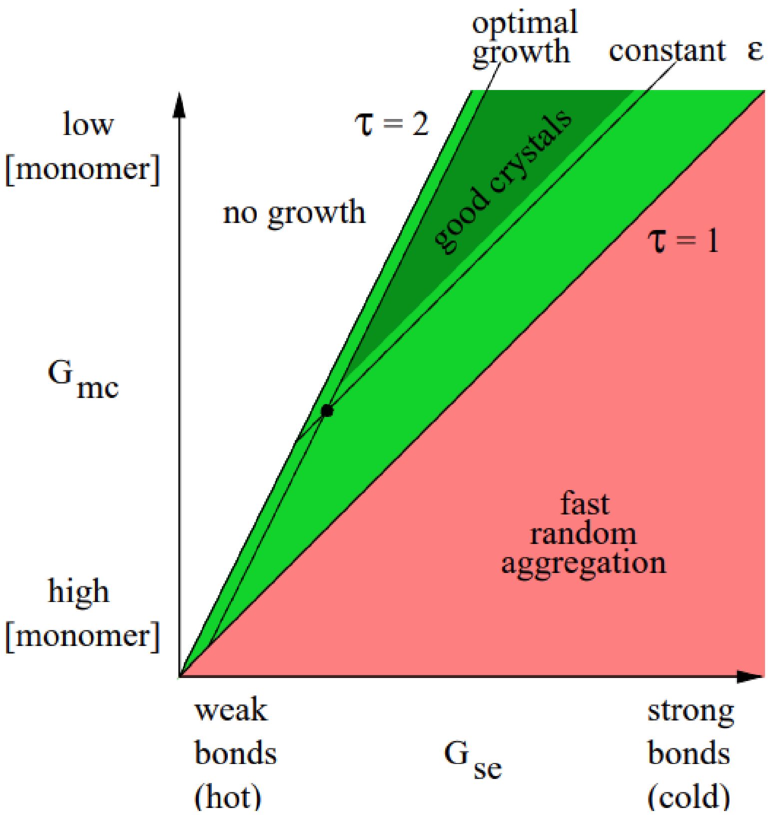

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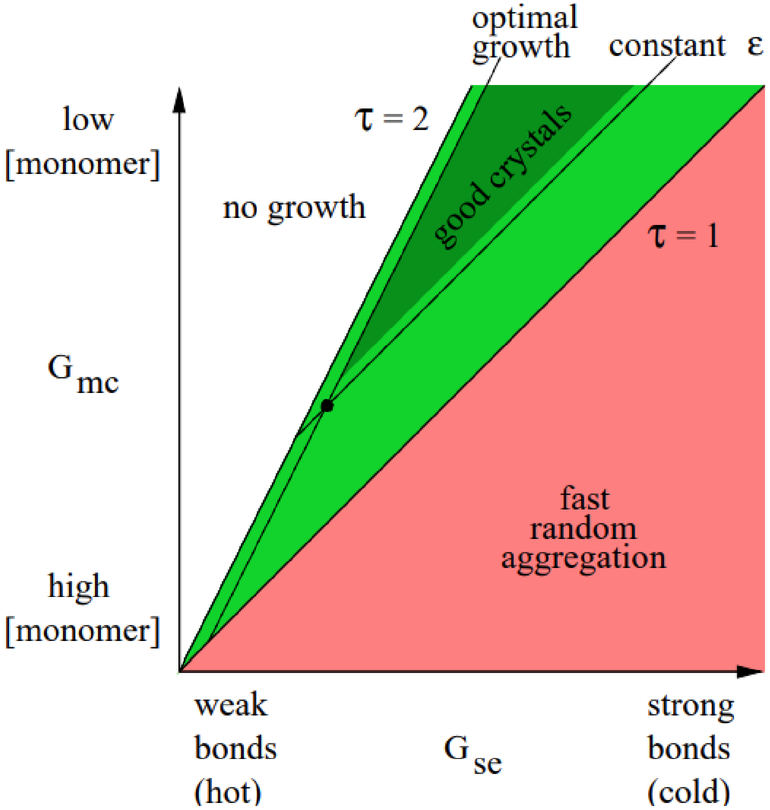
  - make r_f a little larger, and growth is faster, but error rates go up



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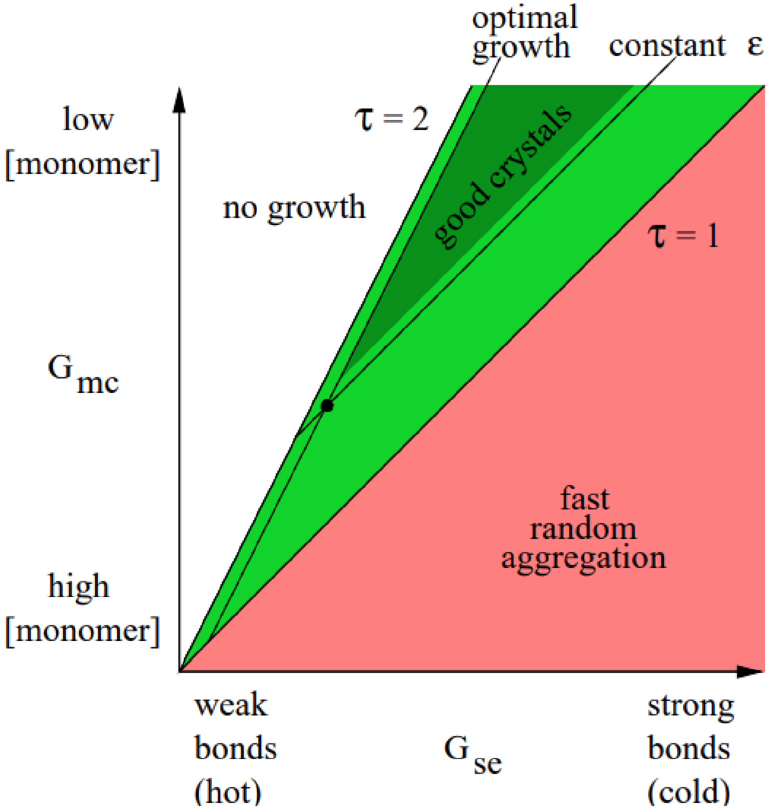
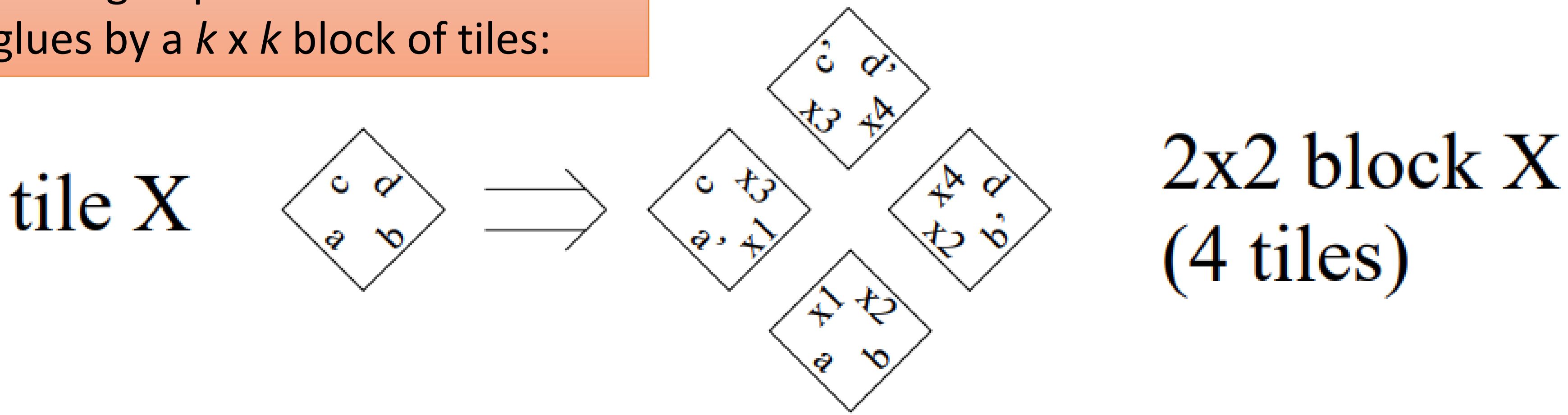
- Intuitively, setting $r_f \approx r_{r,2}$ is like "temperature $\tau = 2$" assembly
  - … but with net zero growth rate
  - make r_f a little larger, and growth is faster, but error rates go up

Theorem [Winfree, 1998]: To have total error rate ε, for fastest assembly speed, set $G_{se} = \ln(4/\varepsilon)$ and $G_{mc} = \ln(8/\varepsilon^2)$, i.e., $G_{mc} = 2G_{se} - \ln 2$, i.e., $r_f/r_{r,2} = 2$



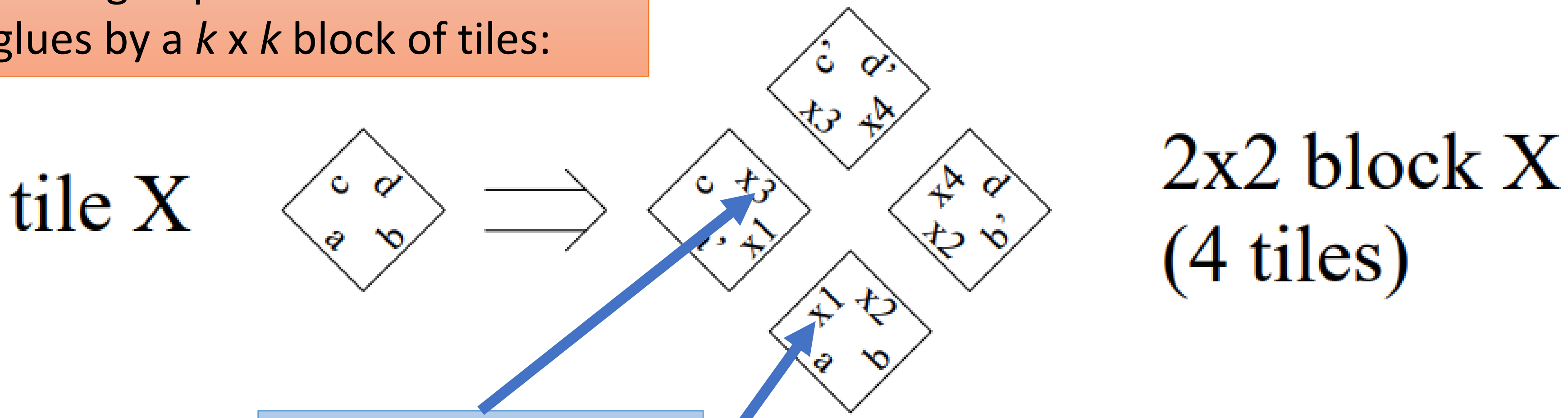
Proofreading: Algorithmic error correction

k x *k* proofreading: replace each tile with all strength-1 glues by a *k* x *k* block of tiles:



Proofreading: Algorithmic error correction

k x *k* proofreading: replace each tile with all strength-1 glues by a *k* x *k* block of tiles:



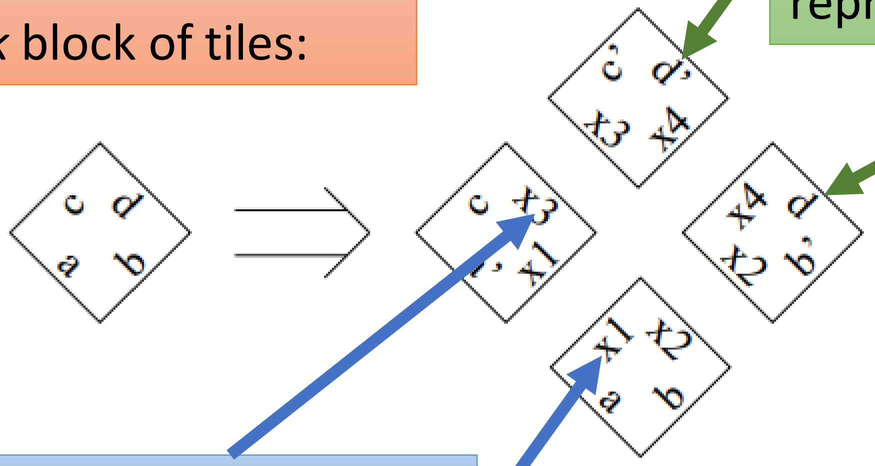
glues internal to the block all unique

Proofreading: Algorithmic error correction

k x *k* proofreading: replace each tile with all strength-1 glues by a *k* x *k* block of tiles:

glues external to the block come in *k* versions that each represent an original glue

tile X



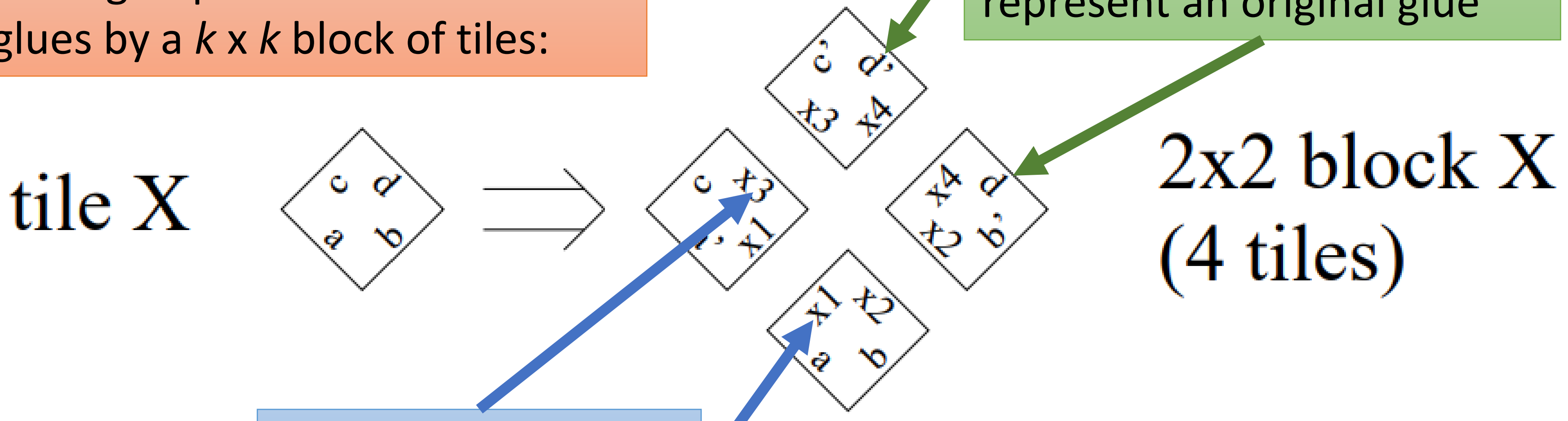
2x2 block X (4 tiles)

glues internal to the block all unique

Proofreading: Algorithmic error correction

k x *k* proofreading: replace each tile with all strength-1 glues by a *k* x *k* block of tiles:

glues external to the block come in *k* versions that each represent an original glue



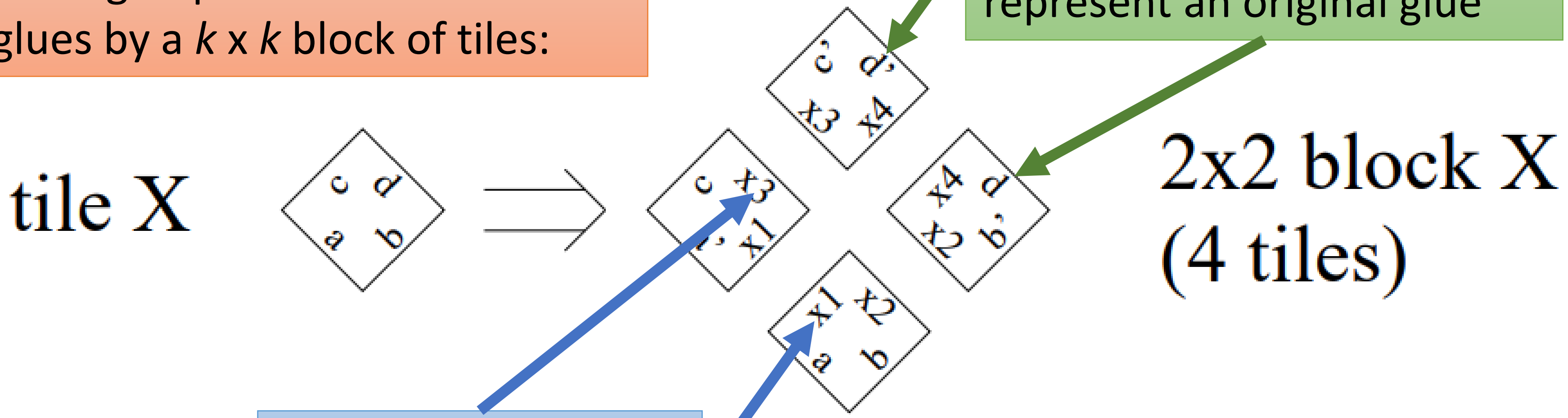
glues internal to the block all unique

Proposition: No tiling of the *k* x *k* region with "consistent external glues" (all represent the same glue in original tile set) has *m* mismatches, where $m \in \{1, 2, \ldots, k-1\}$, i.e., if any mismatch occurs, then at least *k* mismatches occur before the *k* x *k* block can be completed to represent the wrong external glue.

Proofreading: Algorithmic error correction

k x *k* proofreading: replace each tile with all strength-1 glues by a *k* x *k* block of tiles:

glues external to the block come in *k* versions that each represent an original glue



glues internal to the block all unique

Proposition: No tiling of the *k* x *k* region with "consistent external glues" (all represent the same glue in original tile set) has *m* mismatches, where $m \in \{1, 2, \ldots, k-1\}$, i.e., if any mismatch occurs, then at least *k* mismatches occur before the *k* x *k* block can be completed to represent the wrong external glue.

Theorem(ish): If the error rate of the original tile system is ε, the error rate of the *k* x *k* proofreading tile system is $O(\varepsilon^k)$, e.g., if $\varepsilon = 0.01$, then 2 x 2 proofreading gets error rate about $\varepsilon^2 = 0.0001$.

Experimental algorithmic self-assembly

Crystals that think
about how they’re growing

joint work with Damien Woods, Erik Winfree, Cameron Myhrvold, Joy Hui, Felix Zhou, Peng Yin

slides for ECS 289A: Theory of Molecular Computation

Caltech Inria Paris UC Davis Harvard

Acknowledgements

Caltech

Inria Paris

UC Davis

Harvard

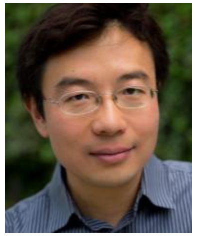
Damien Woods
(co-first author)

Erik Winfree

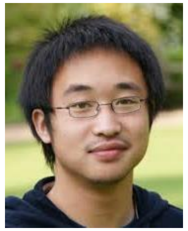
<u>co-authors</u>

Cameron Myhrvold

Peng Yin



Felix Zhou



Joy Hui

<u>lab/science help</u>

Sungwook Woo
Constantine Evans
Sarina Mohanty
Niranjan Srinivas
Deborah Fygenson
Yannick Rondolez
Mingjie Dai
Nikhil Gopalkrishnan
Chris Thachuk
Nadine Dabby
Jongmin Kim
Paul Rothemund
Bryan Wei
Cody Geary
Ashwin Gopinath

Diverse and robust molecular algorithms using reprogrammable DNA self-assembly. Damien Woods†, David Doty†, Cameron Myhrvold, Joy Hui, Felix Zhou, Peng Yin, Erik Winfree. <u>Nature</u> 2019. †*These authors contributed equally*.

Hierarchy of abstractions

Bits:	**Boolean circuits compute**
Tiles:	Tile growth implements circuits
DNA:	DNA strands implement tiles

Harmonious arrangement

0

1

1

0

1

1

Harmonious arrangement

0

1

1

0

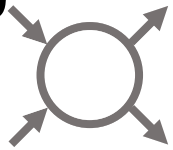
1

1

Harmonious arrangement

0	1
1	1
1	1
0	1
1	0
1	0

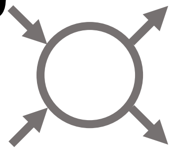
Harmonious arrangement



0	1
1	1
1	1
0	1
1	0
1	0

Harmonious arrangement

0 1



1 0

1

0

1

1

1

1

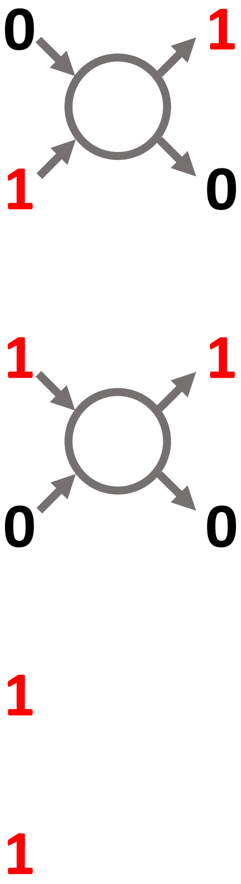
1

1

0

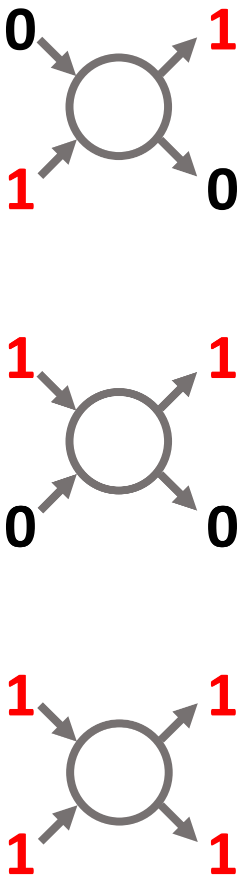
0

Harmonious arrangement



1
1
1
1
0
0

Harmonious arrangement



1

1

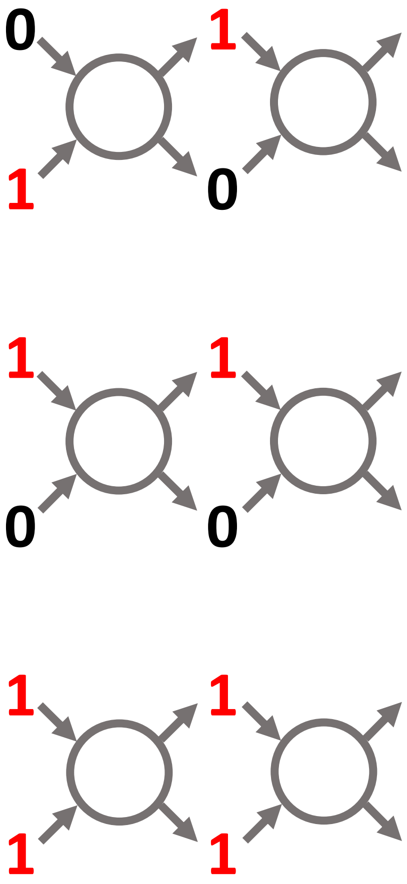
1

1

0

0

Harmonious arrangement



1

1

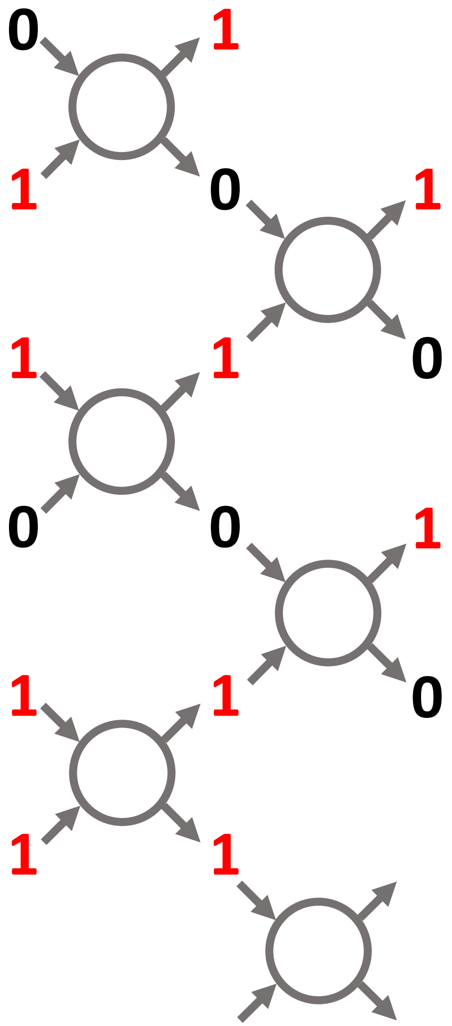
1

1

0

0

Harmonious arrangement



1

1

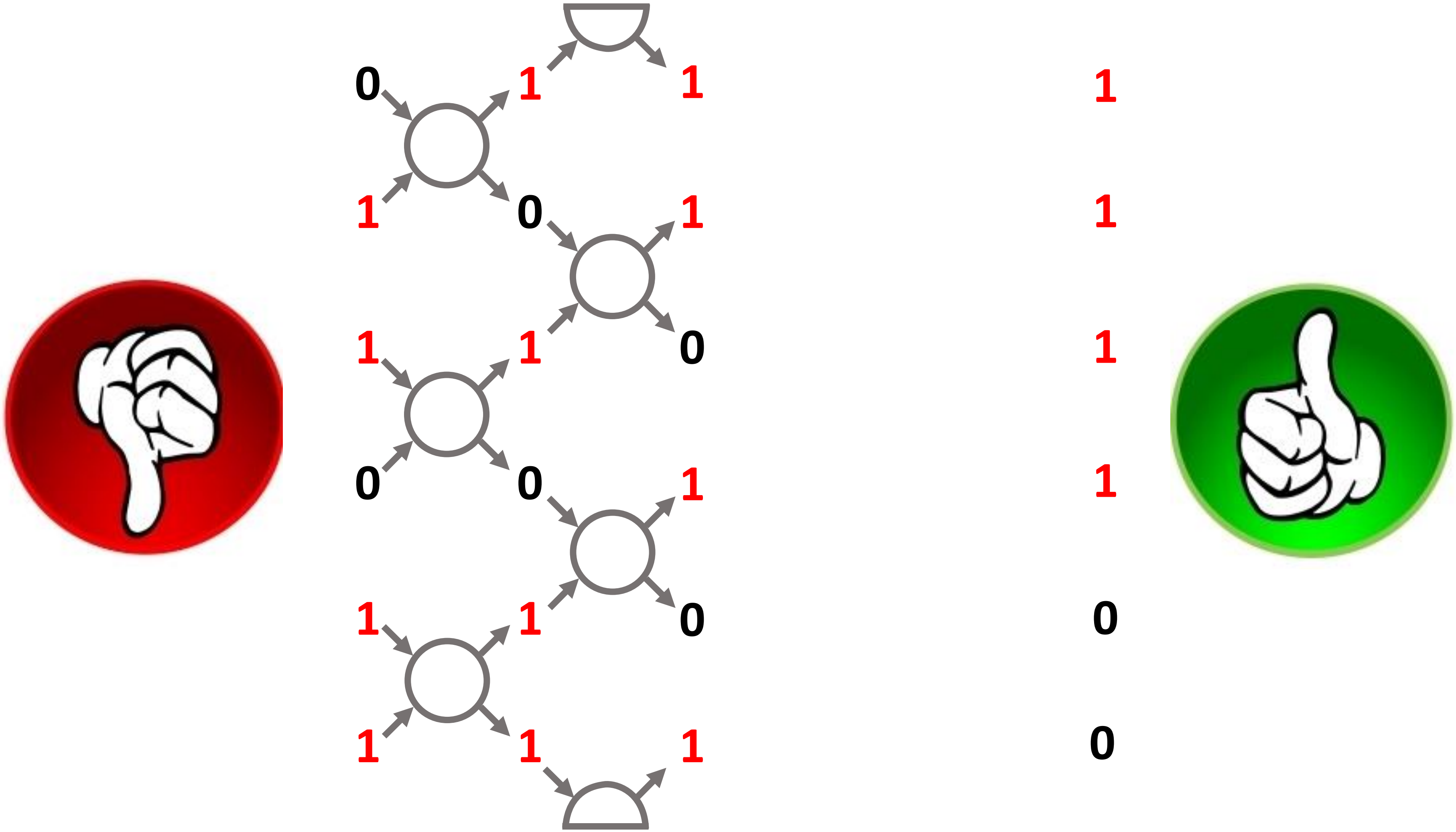
1

1

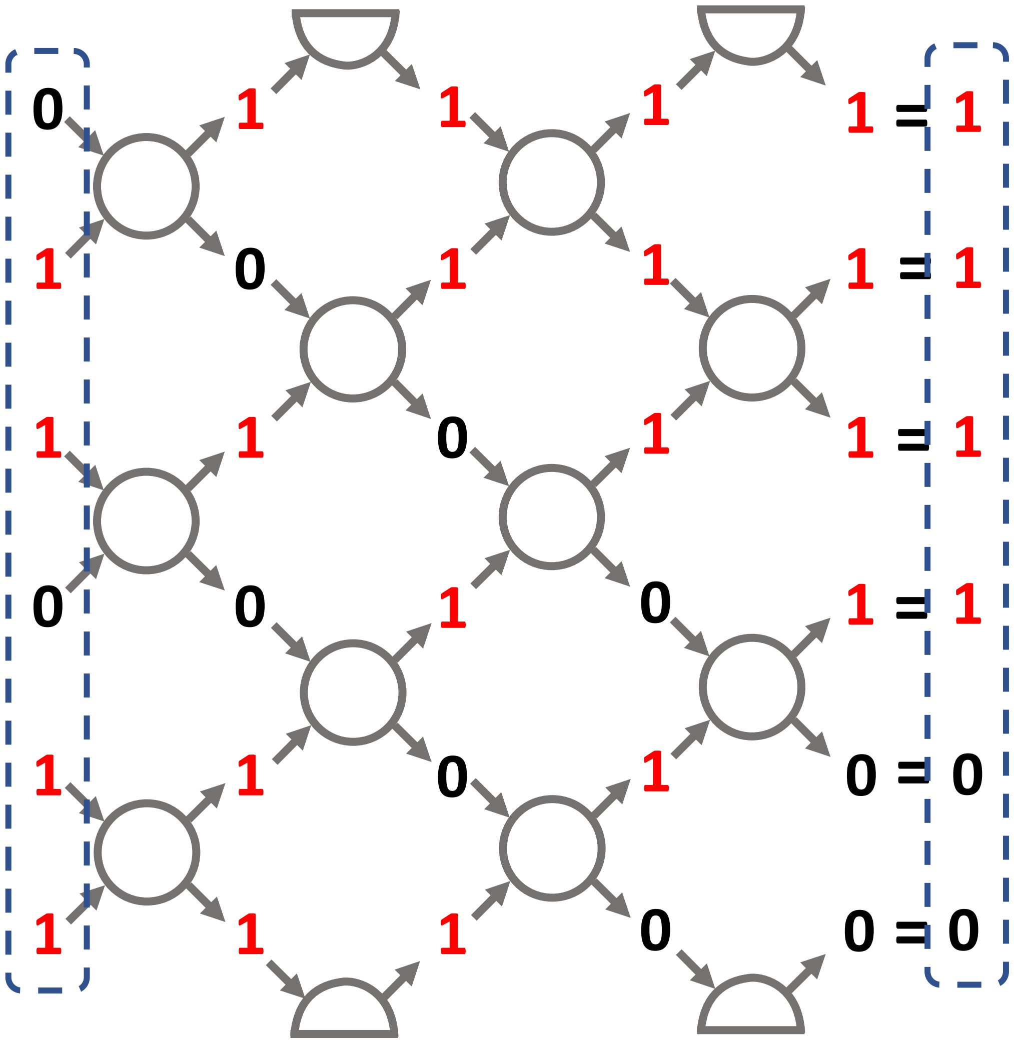
0

0

Harmonious arrangement



Harmonious arrangement



a.k.a. sorting

Odd bits

1

0

1

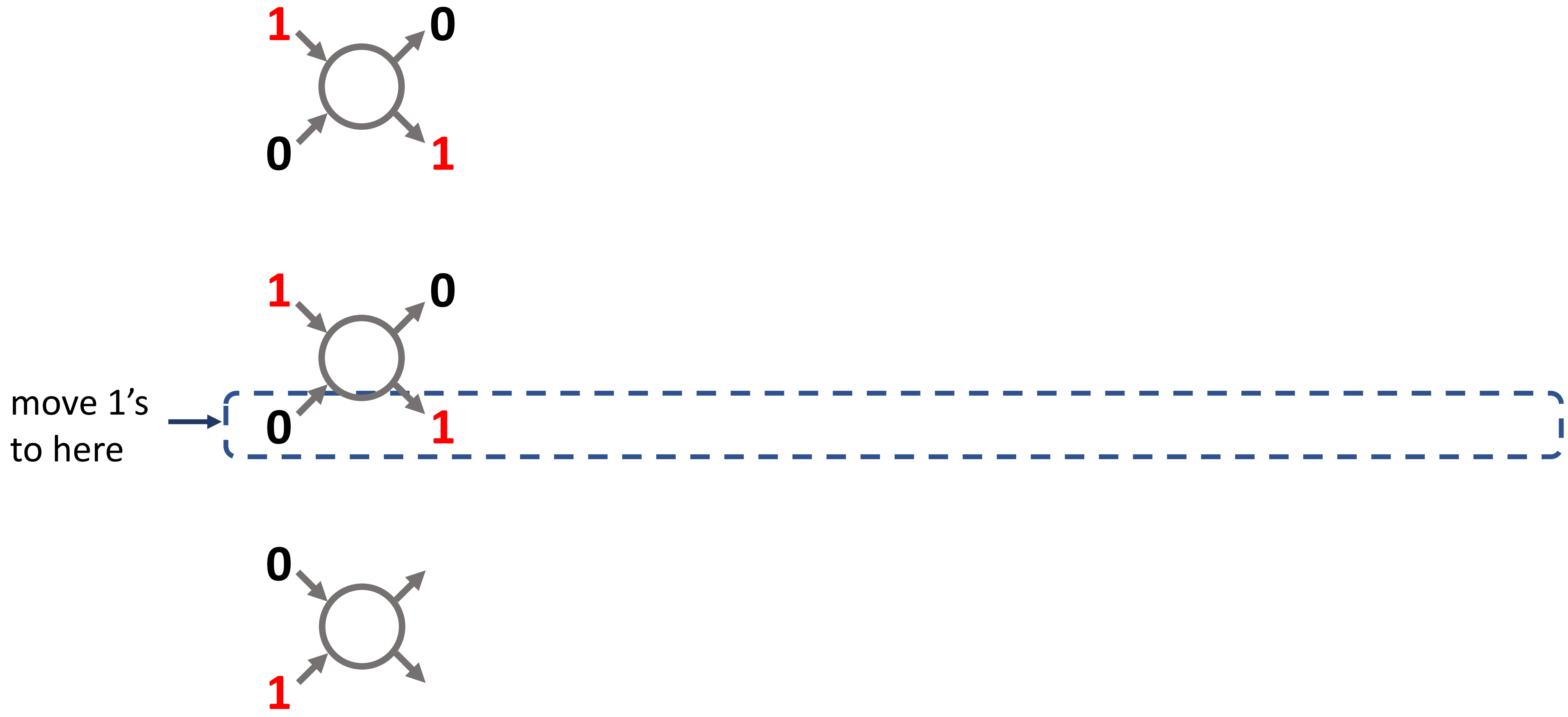
0

0

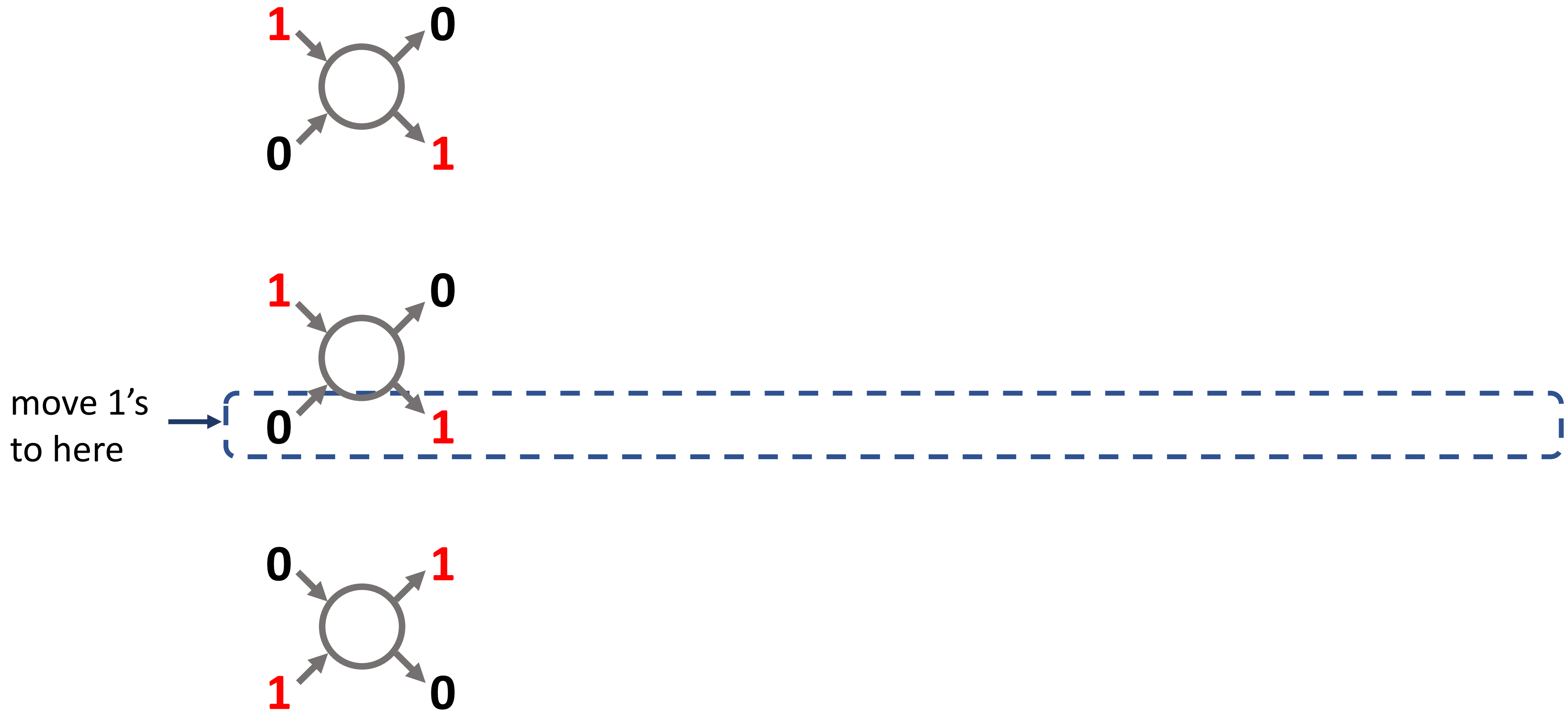
1

Odd bits

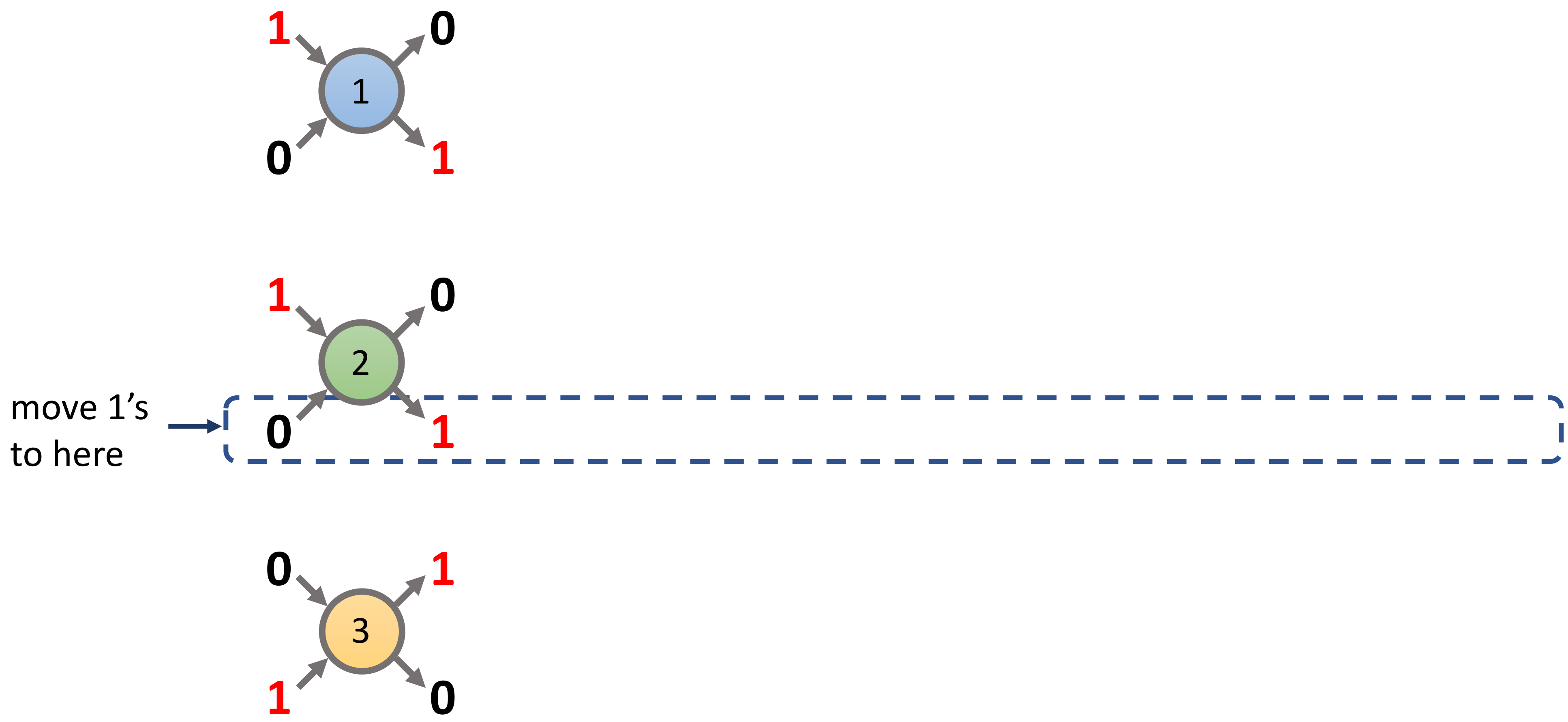
Odd bits



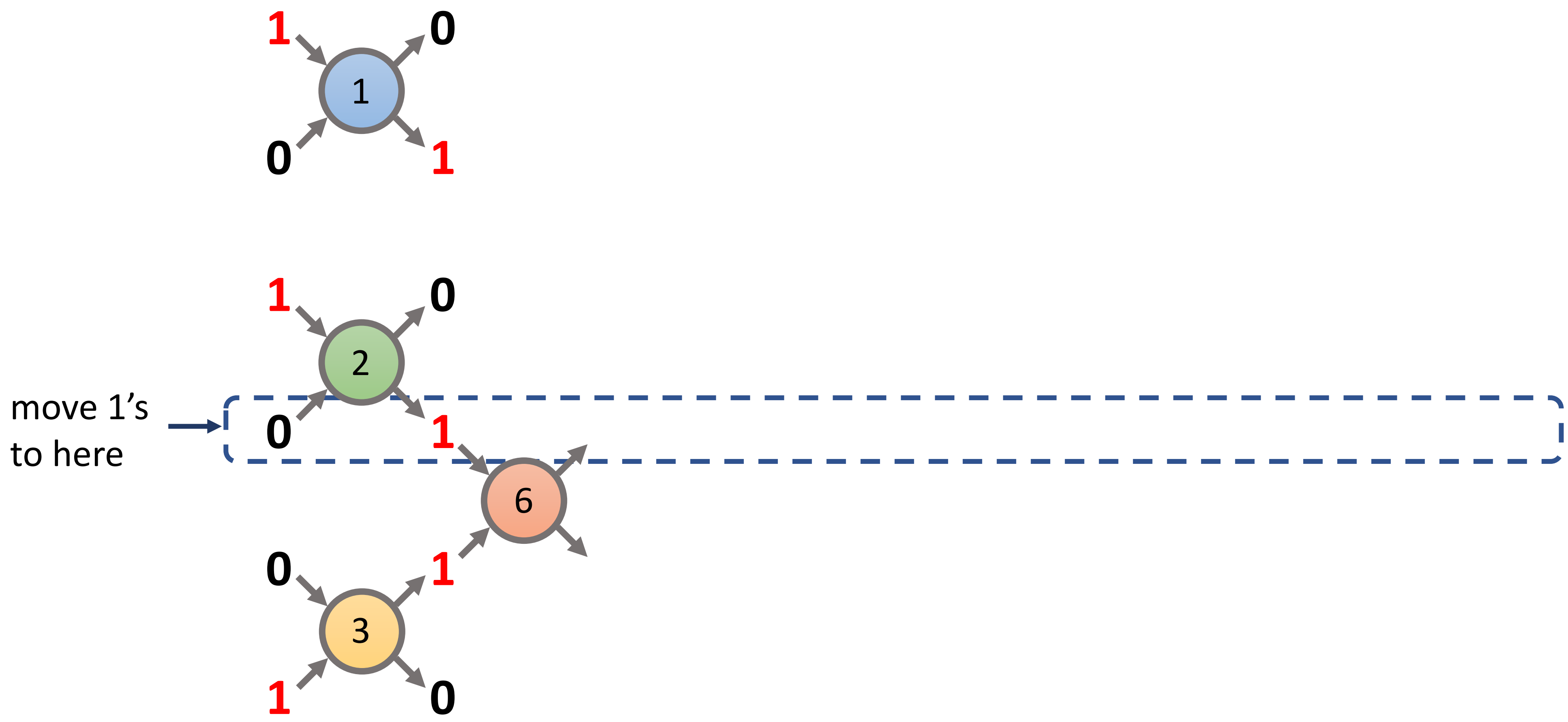
Odd bits



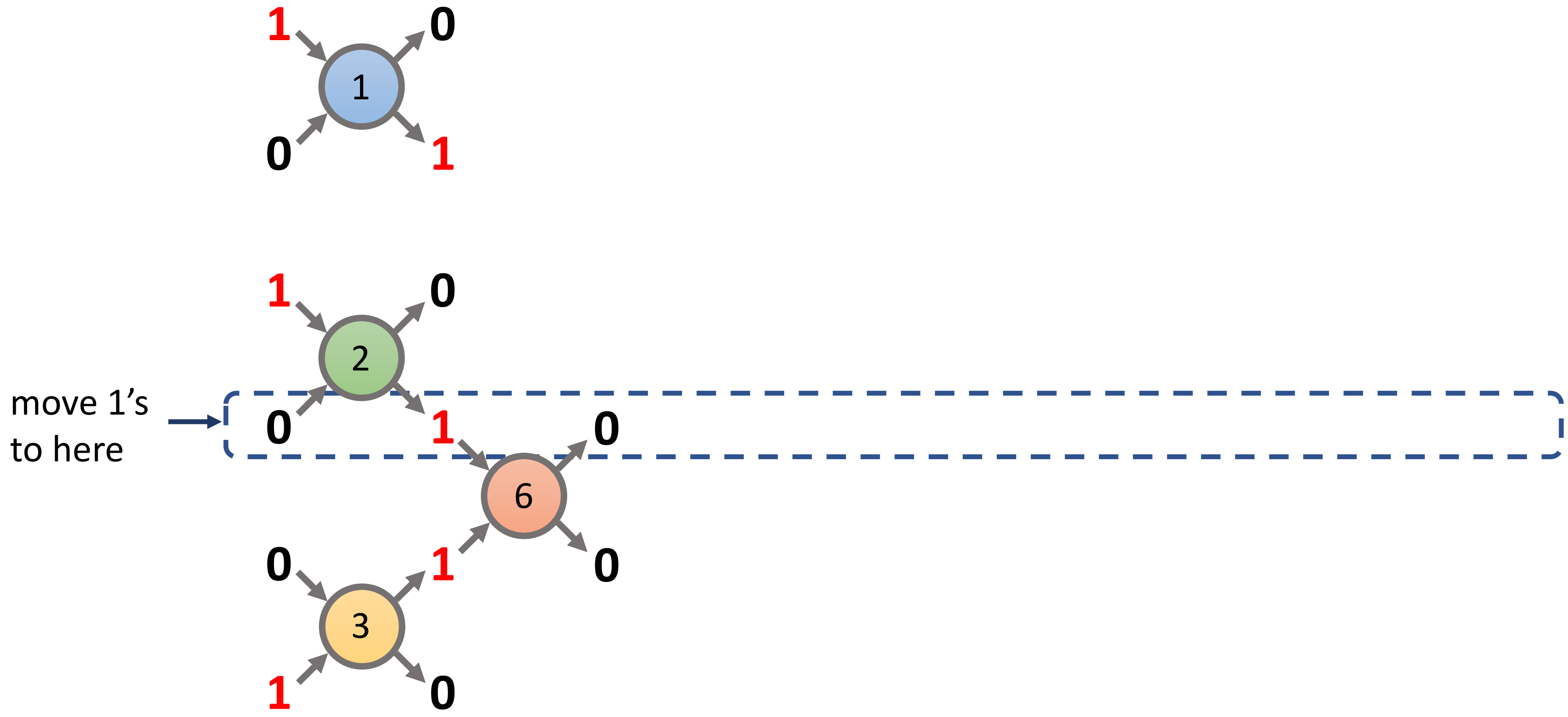
Odd bits



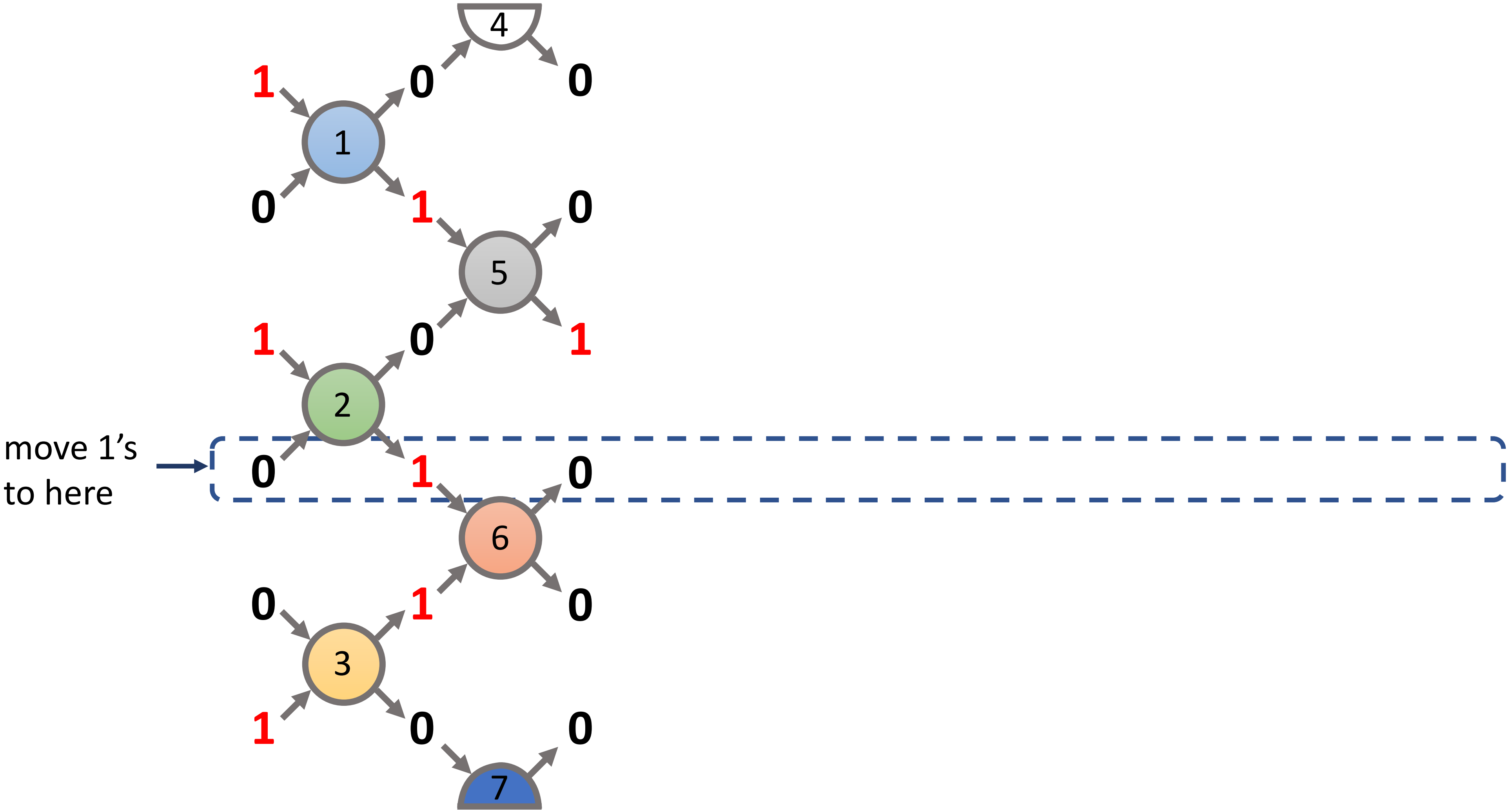
Odd bits



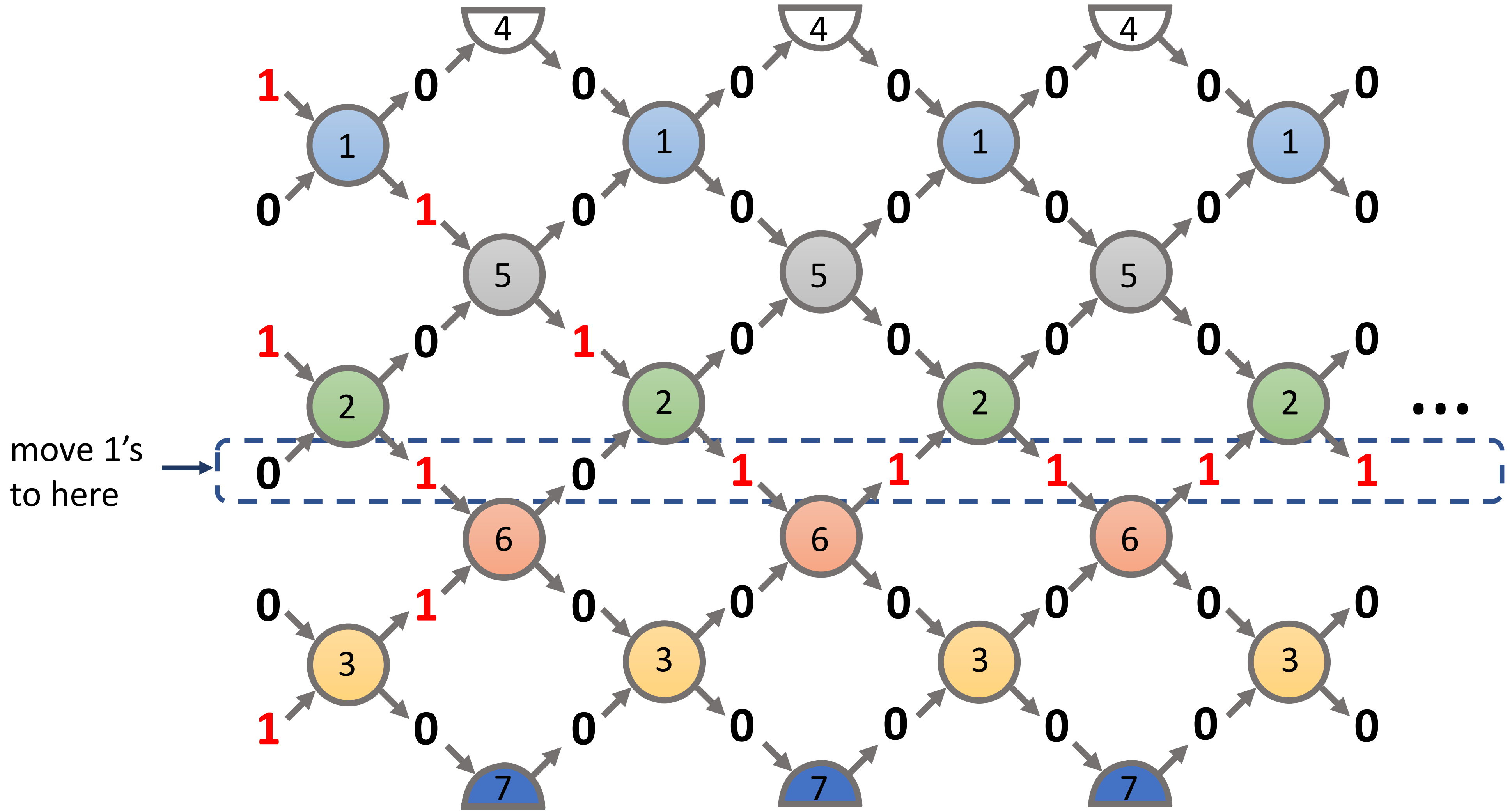
Odd bits



Odd bits



Odd bits a.k.a. parity



Parity

1

0

1

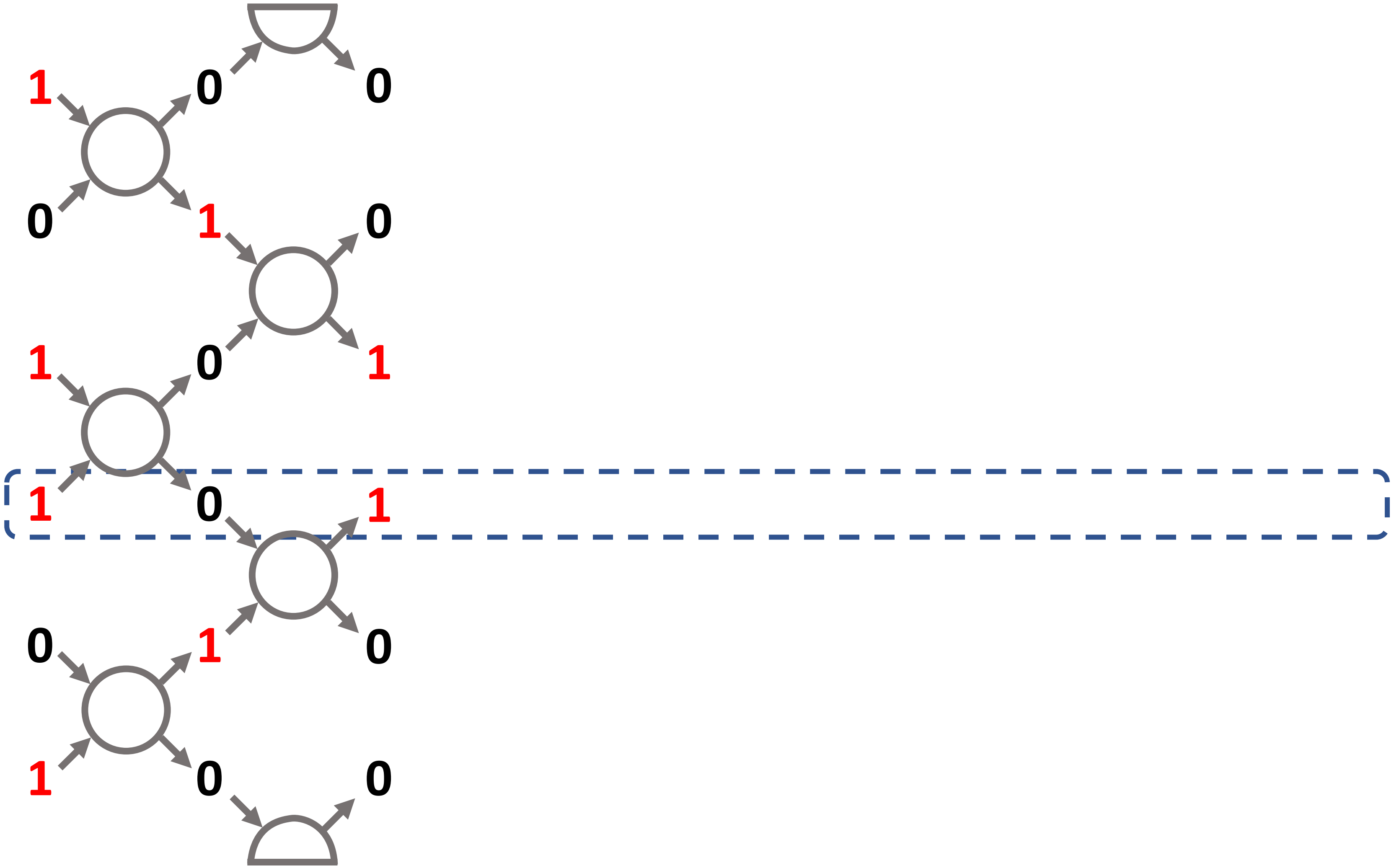
1

0

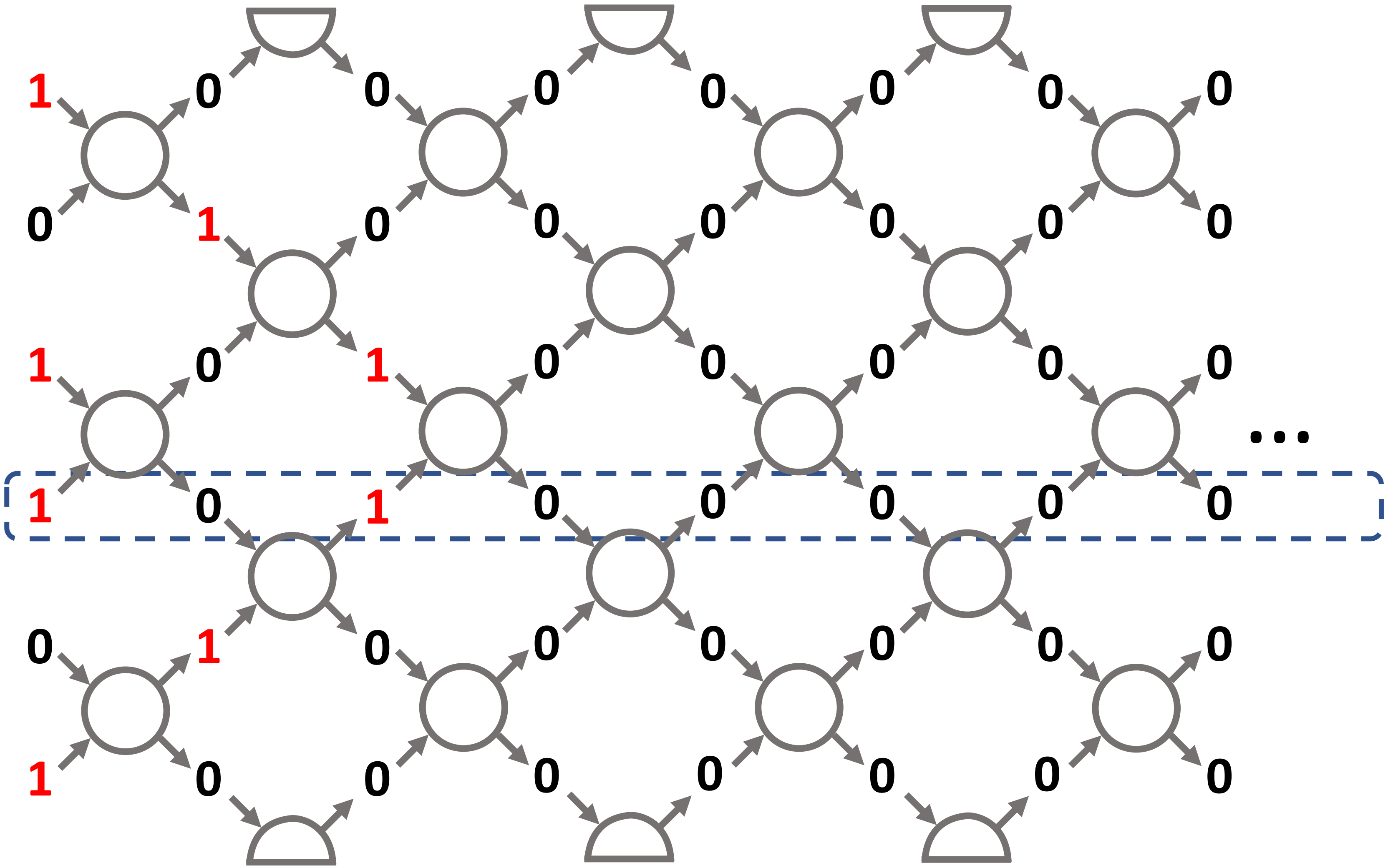
1

Parity

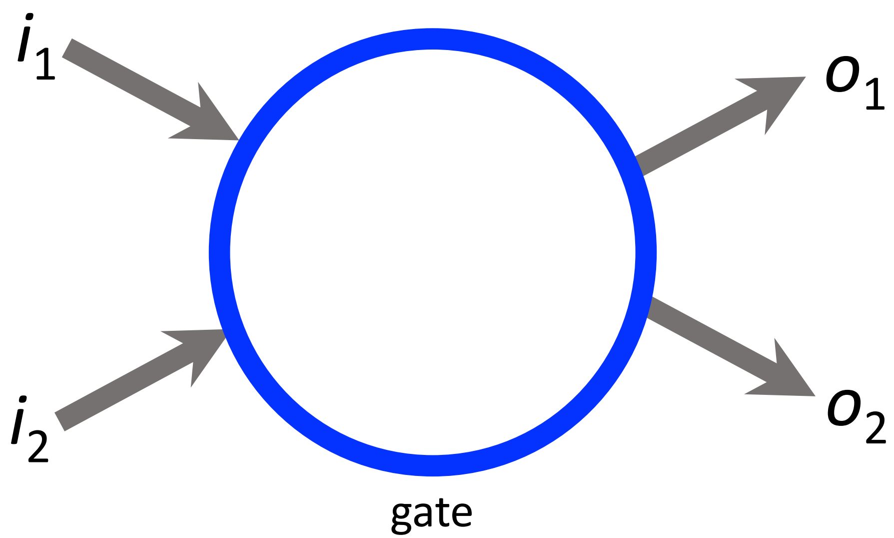
Parity



Parity

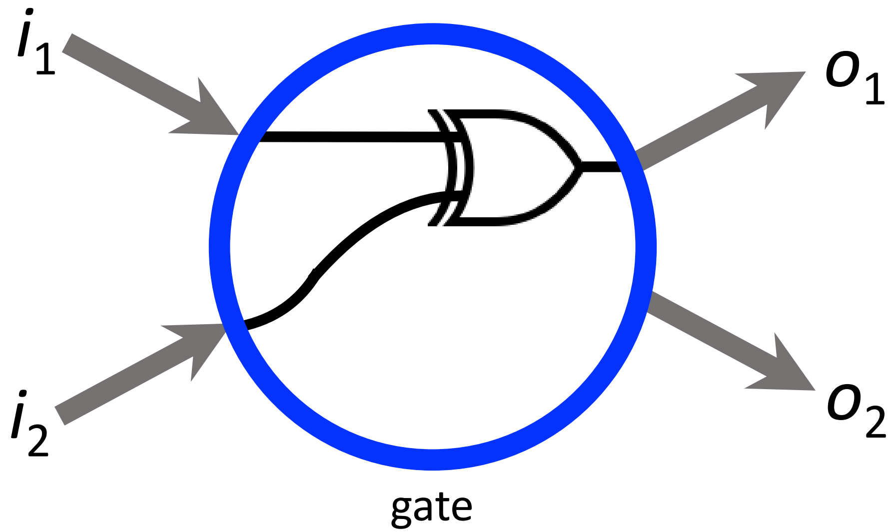


Circuit model



gate: function with two input bits i_1,i_2
and <u>two</u> output bits o_1,o_2

Circuit model

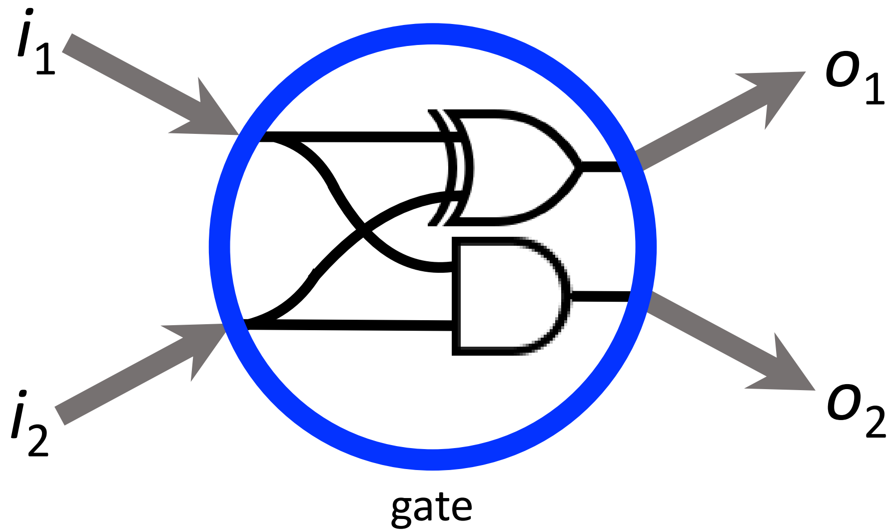


truth table

i_1	i_2	o_1	o_2
0	0	0	
0	1	1	
1	0	1	
1	1	0	

gate: function with two input bits i_1,i_2
and <u>two</u> output bits o_1,o_2

Circuit model

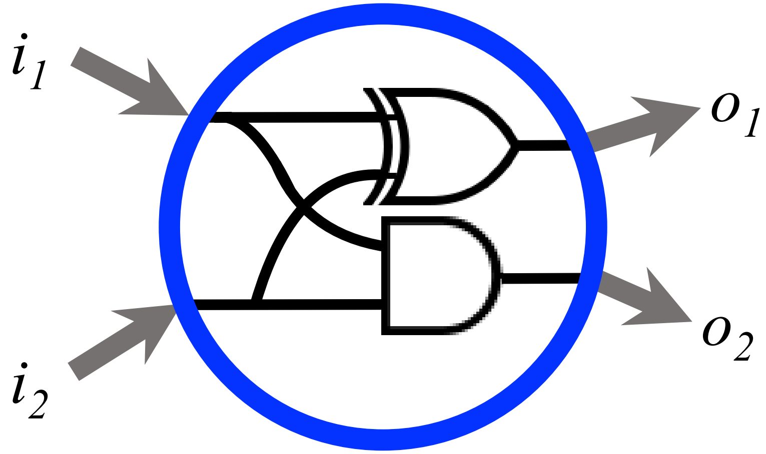


truth table

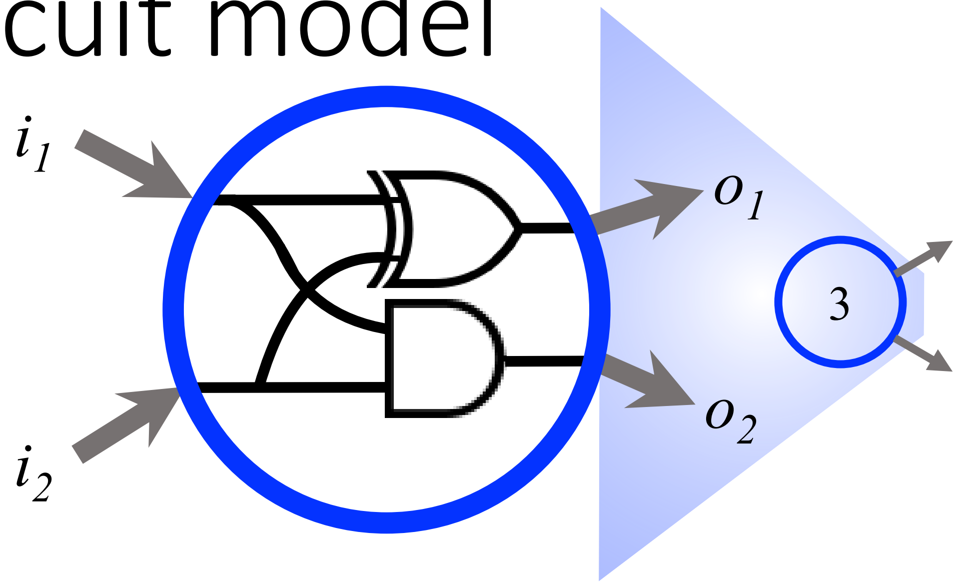
i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1

gate: function with two input bits i_1,i_2
and <u>two</u> output bits o_1,o_2

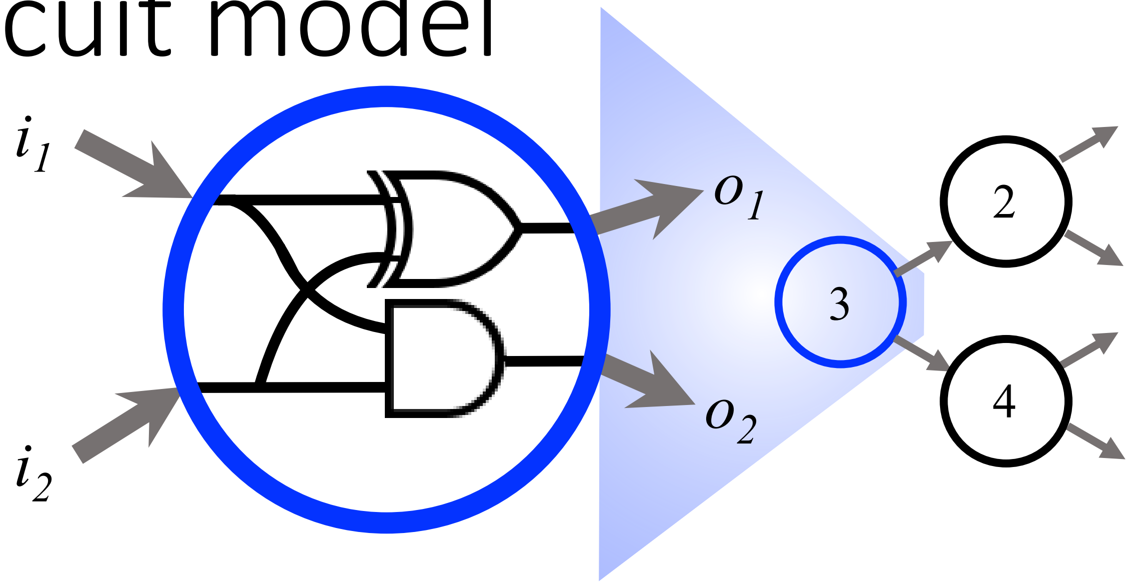
Circuit model



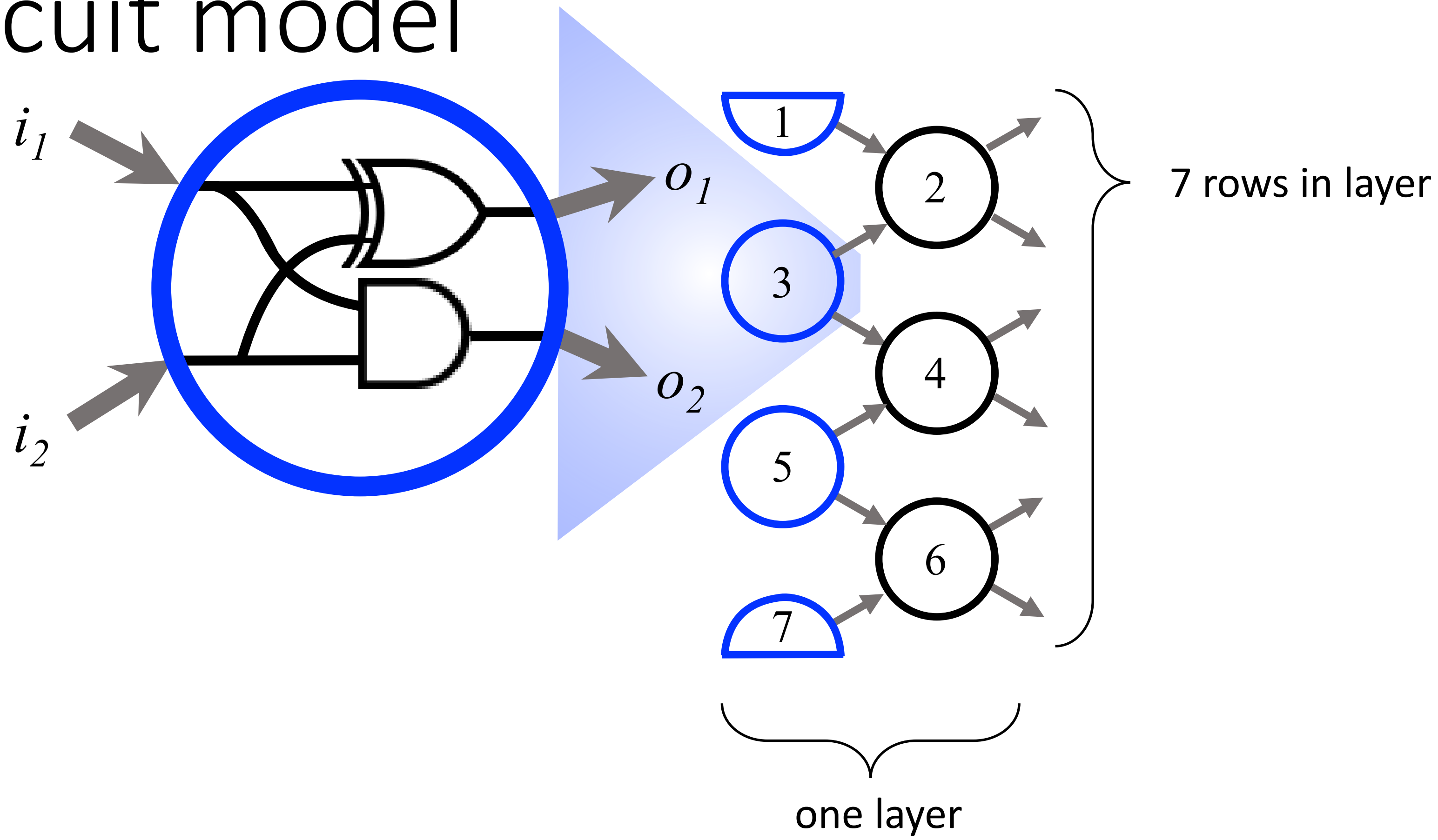
Circuit model



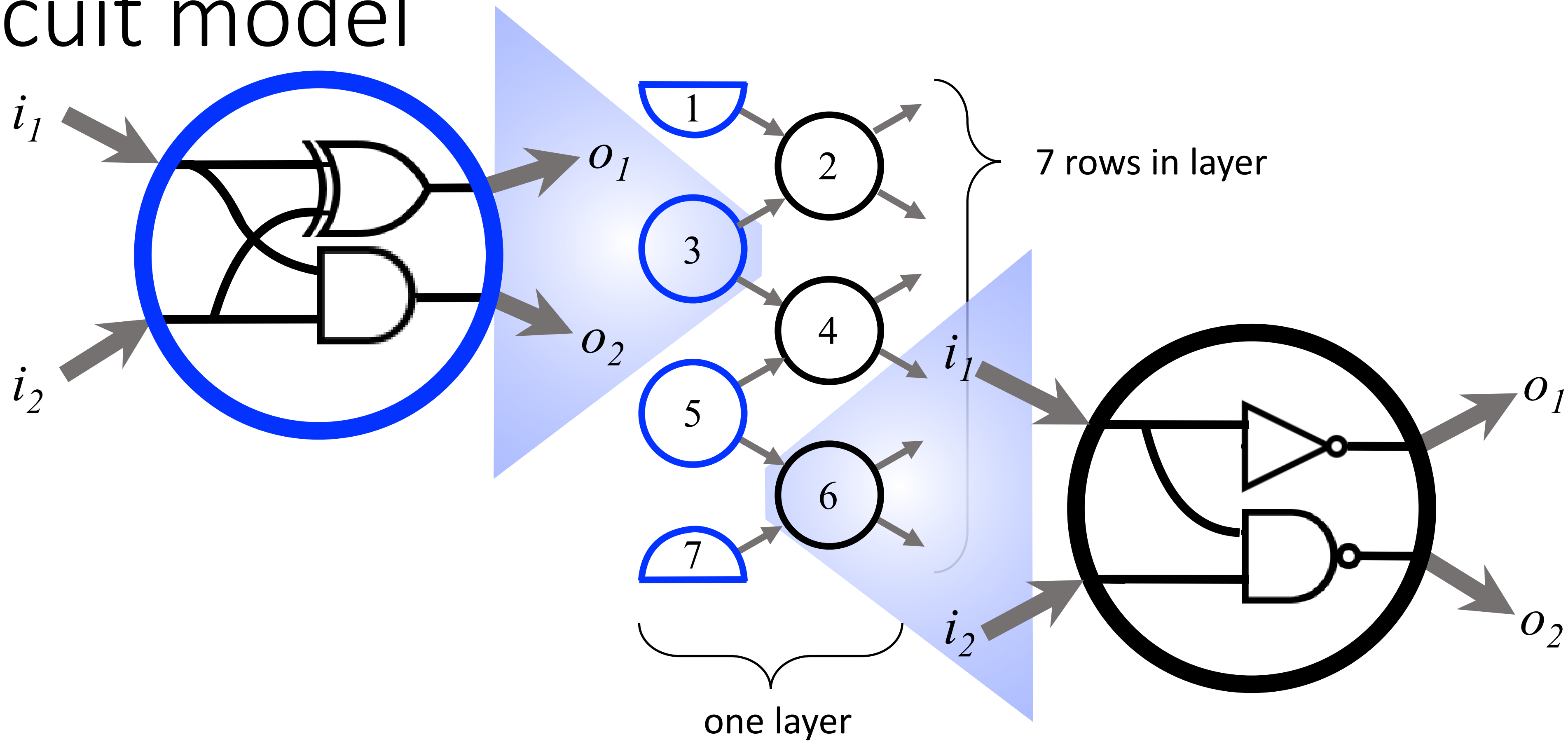
Circuit model



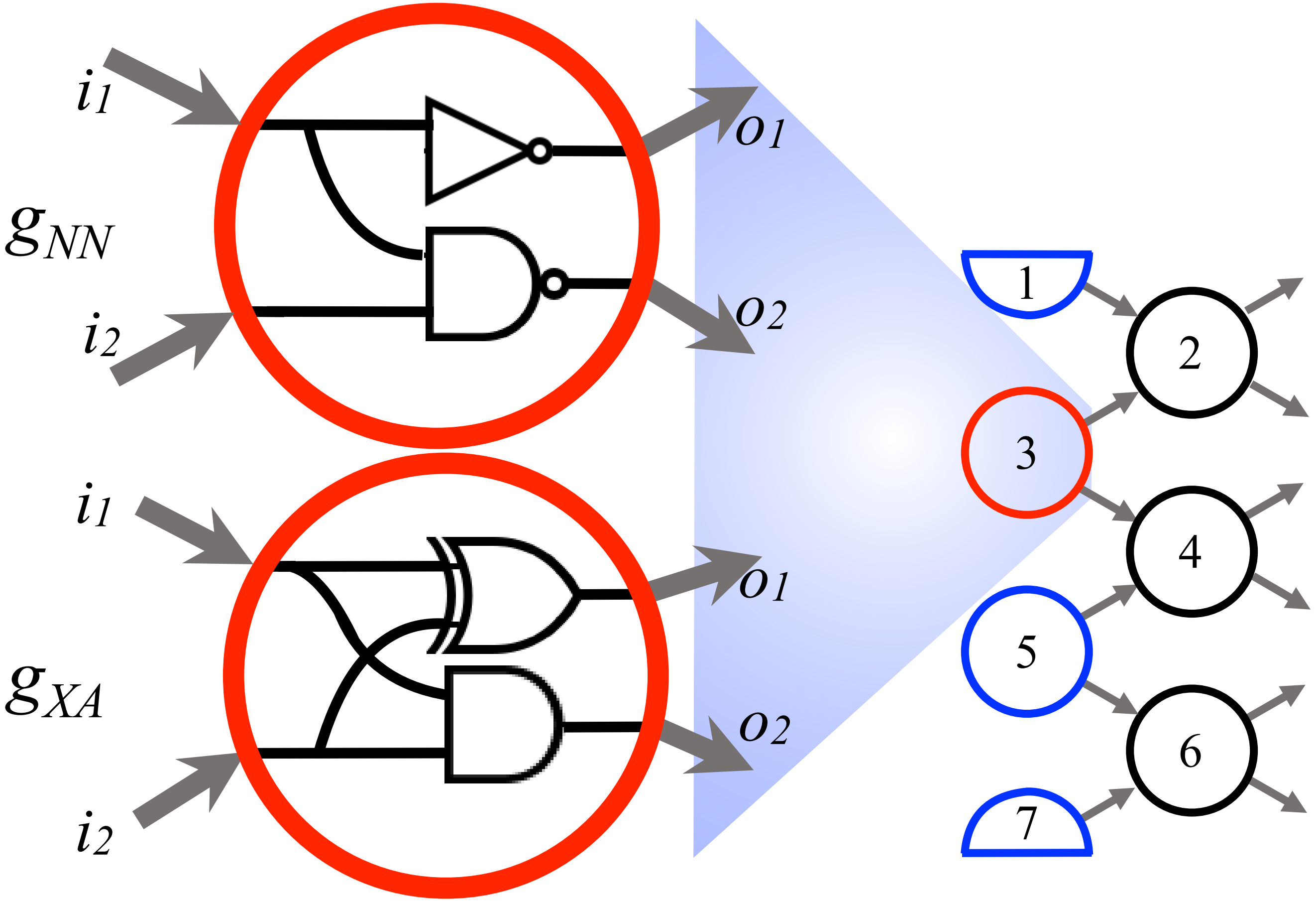
Circuit model



Circuit model



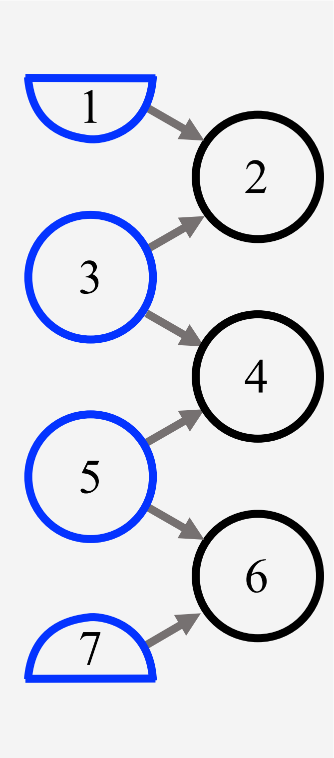
Circuit model



Randomization: Each row may be assigned ≥ 2 gates, with associated probabilities, e.g., Pr[g_{NN}] = Pr[g_{XA}] = ½

Circuit model

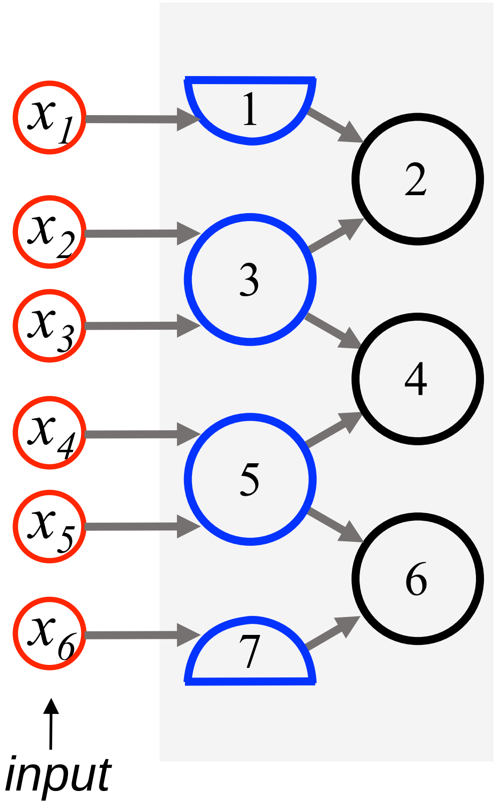
Programmer specifies layer:
gates to go in each row



Circuit model

Programmer specifies layer: gates to go in each row

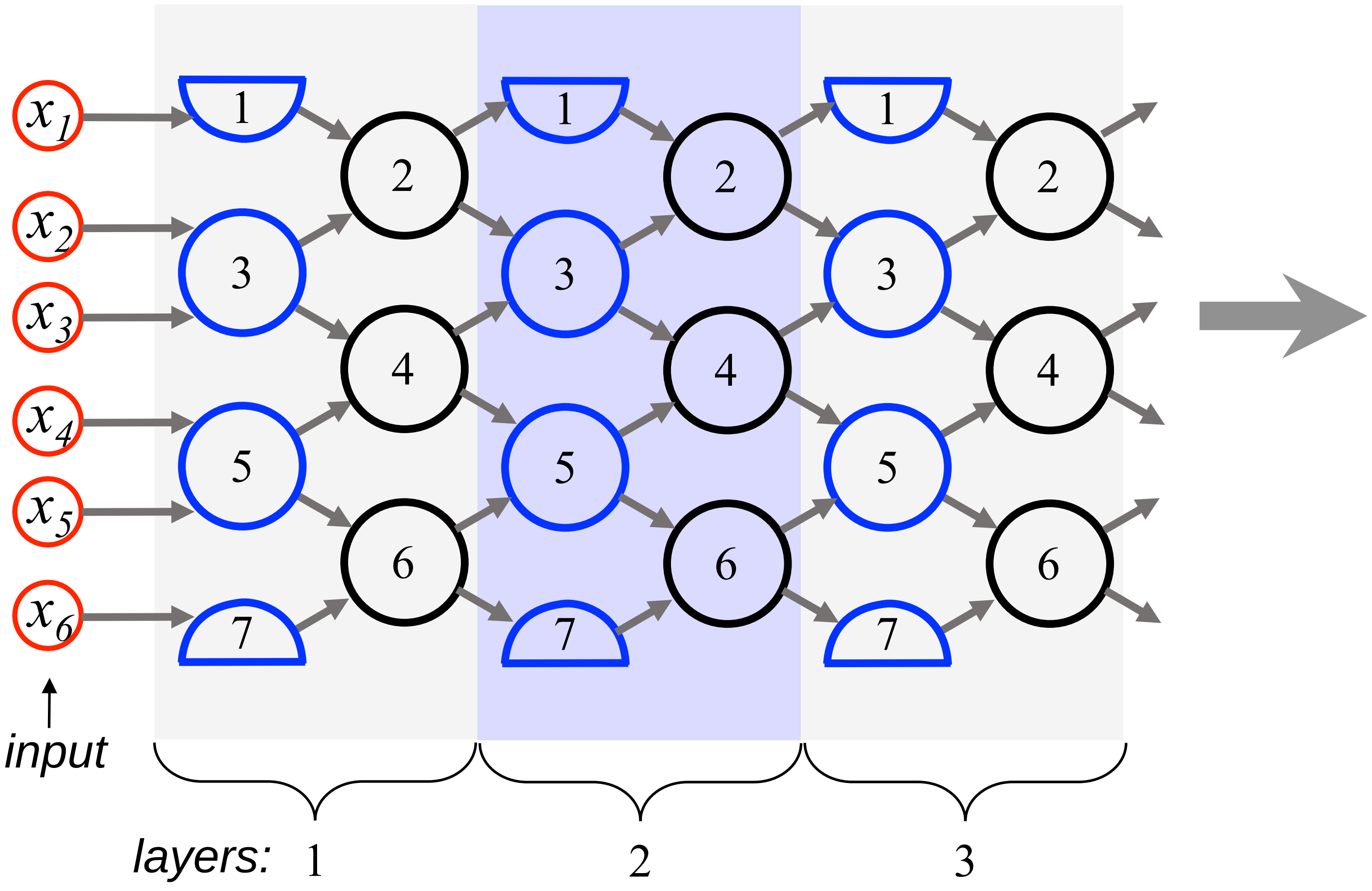
User gives n input bits



Circuit model

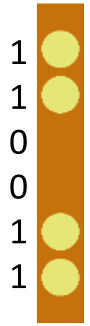
Programmer specifies layer: gates to go in each row

User gives n input bits

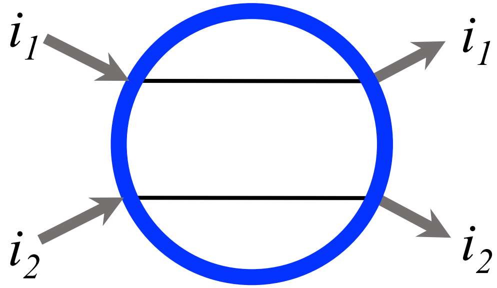


Example circuits with same gate in every row

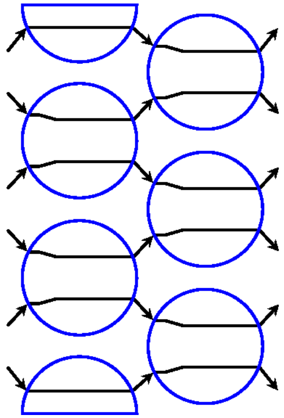
COPY



COPY gates

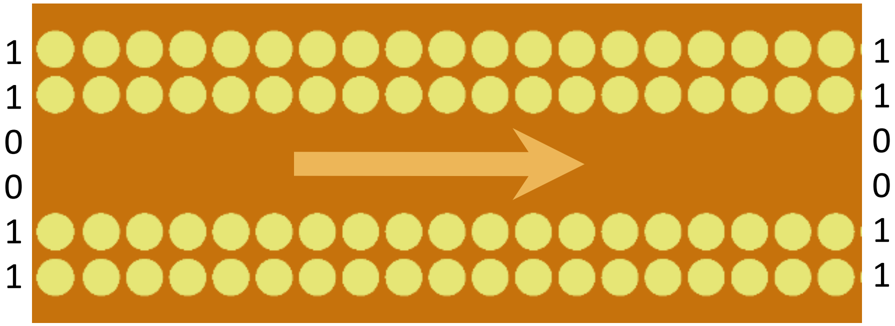


i_1	i_2	o_1	o_2
0	0	0	0
0	1	0	1
1	0	1	0
1	1	1	1

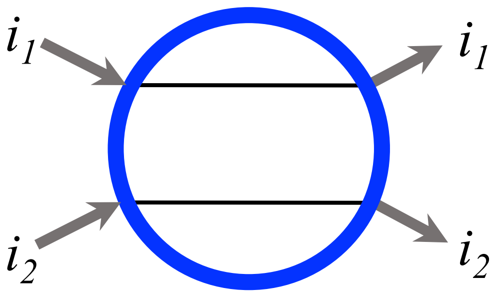


Example circuits with same gate in every row

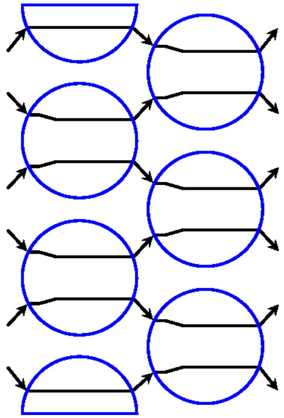
COPY



COPY gates

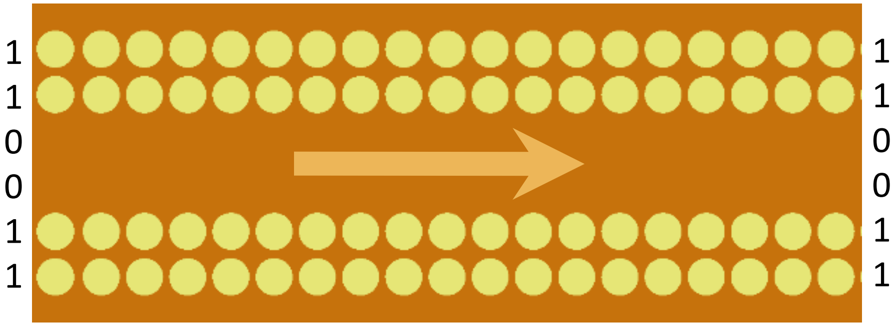


i_1	i_2	o_1	o_2
0	0	0	0
0	1	0	1
1	0	1	0
1	1	1	1

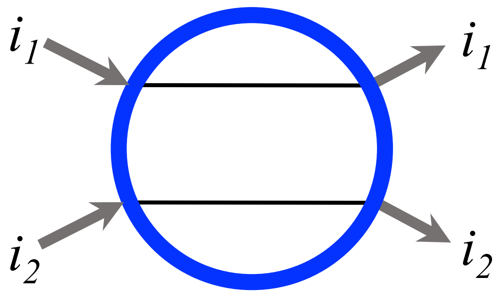


Example circuits with same gate in every row

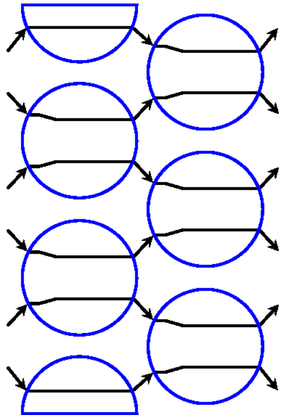
COPY



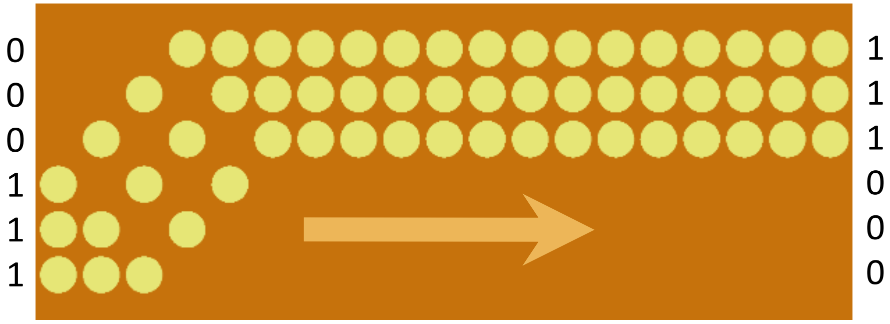
COPY gates



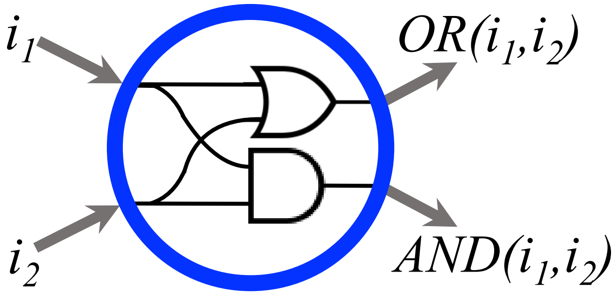
i_1	i_2	o_1	o_2
0	0	0	0
0	1	0	1
1	0	1	0
1	1	1	1



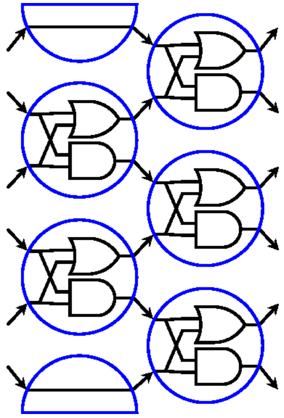
SORTING



SORTING gates

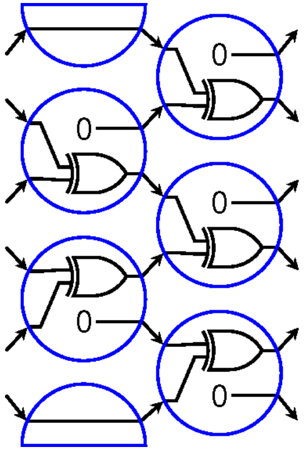


i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	1	1



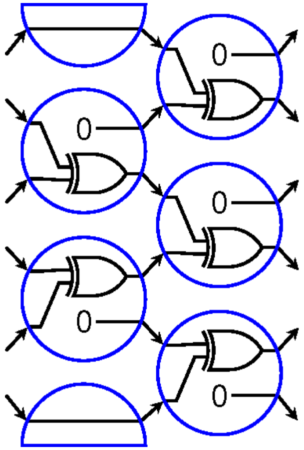
Example circuits with different gates in each row

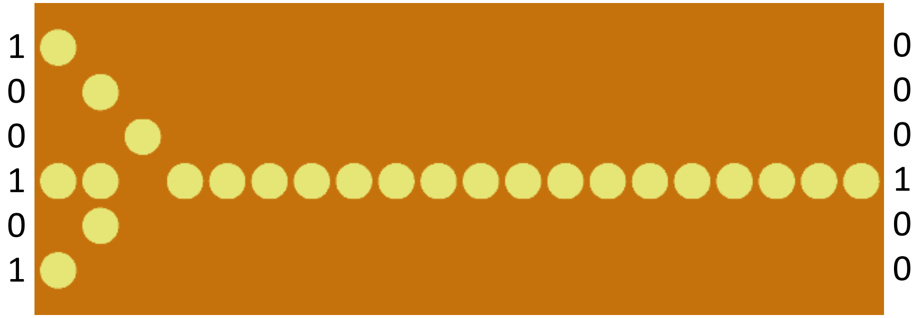
PARITY



Example circuits with different gates in each row

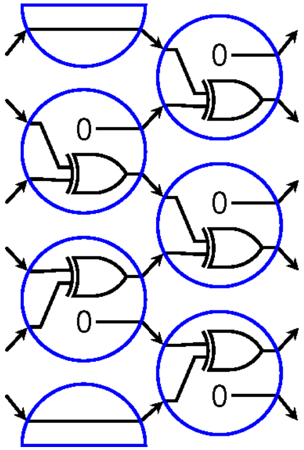
PARITY

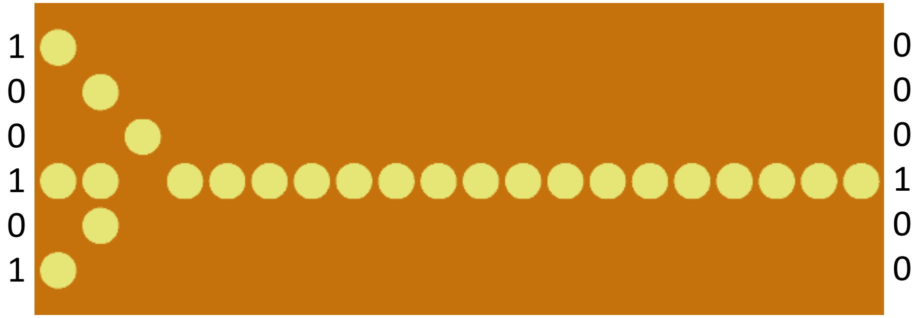




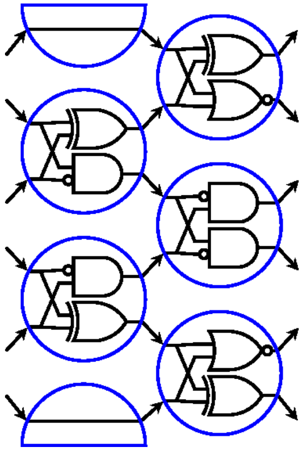
Example circuits with different gates in each row

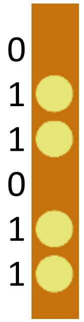
PARITY





MULTIPLEOF3

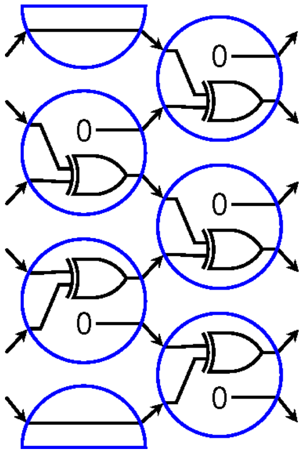


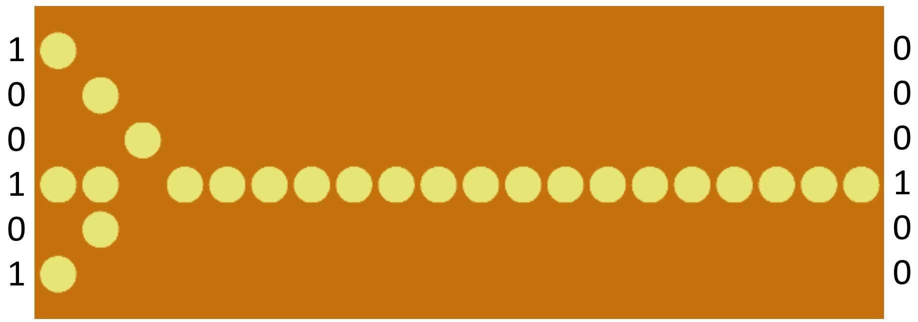


011011_2

Example circuits with different gates in each row

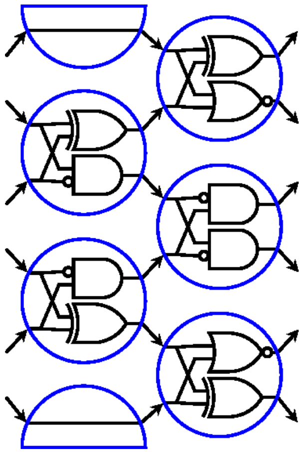
PARITY

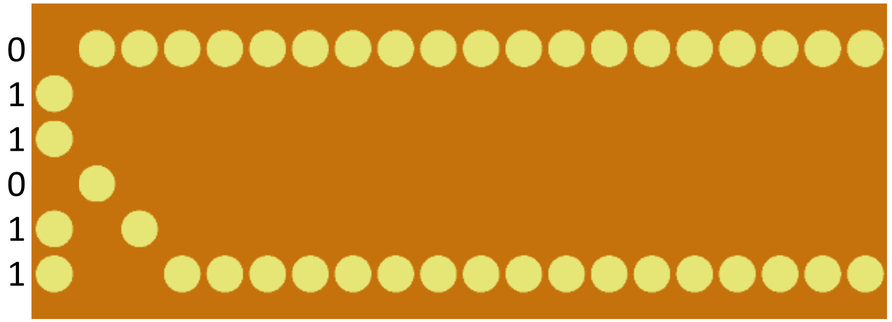




MULTIPLEOF3

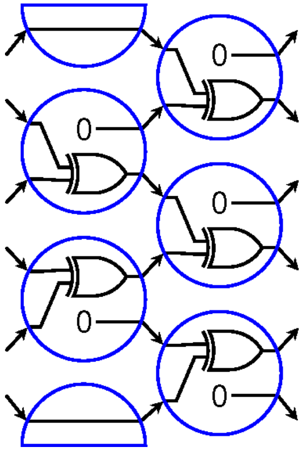
$011011_2 = 27_{10} = 3 \cdot 9$

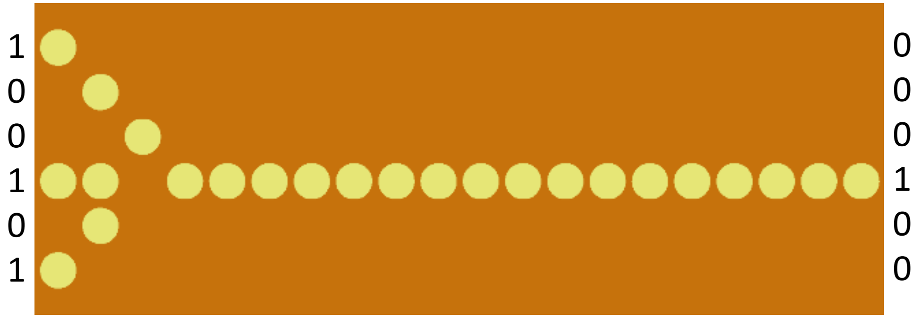




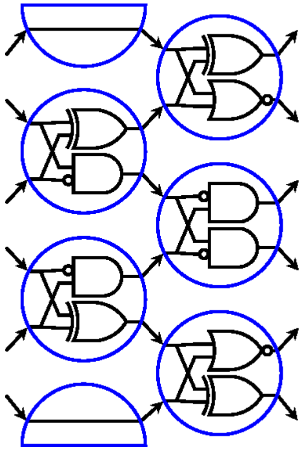
Example circuits with different gates in each row

PARITY

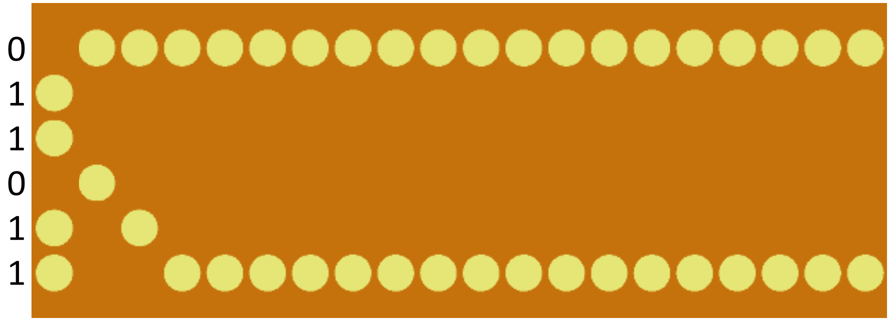




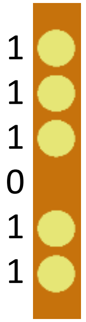
MULTIPLEOF3



$011011_2 = 27_{10} = 3\cdot9$

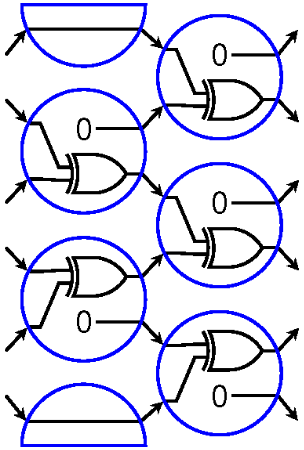


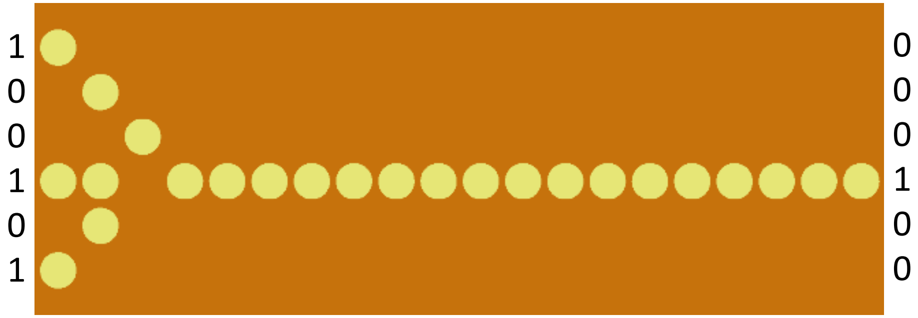
111011_2



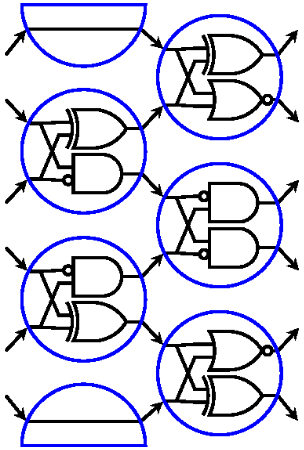
Example circuits with different gates in each row

PARITY

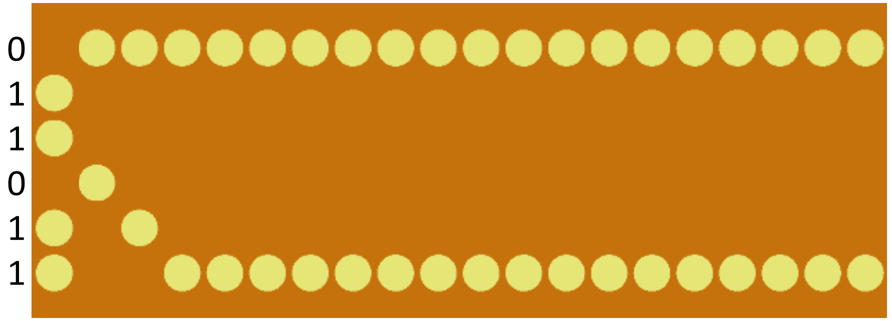




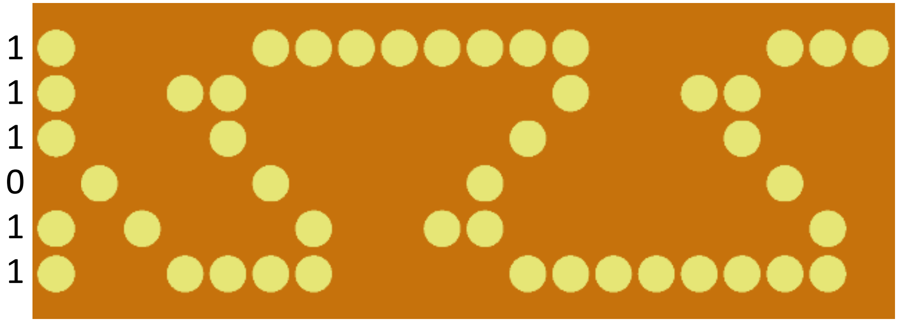
MULTIPLEOF3



$011011_2 = 27_{10} = 3 \cdot 9$

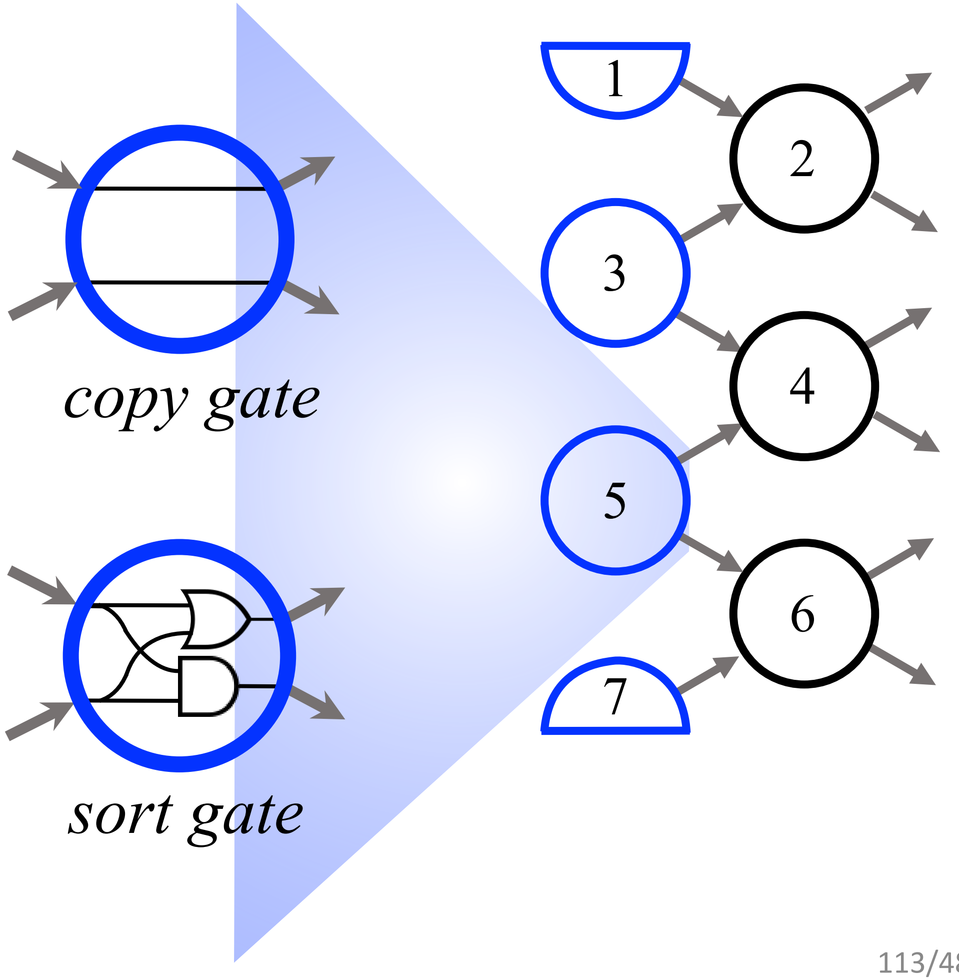


$111011_2 = 59_{10} = 3 \cdot 19 + 2$

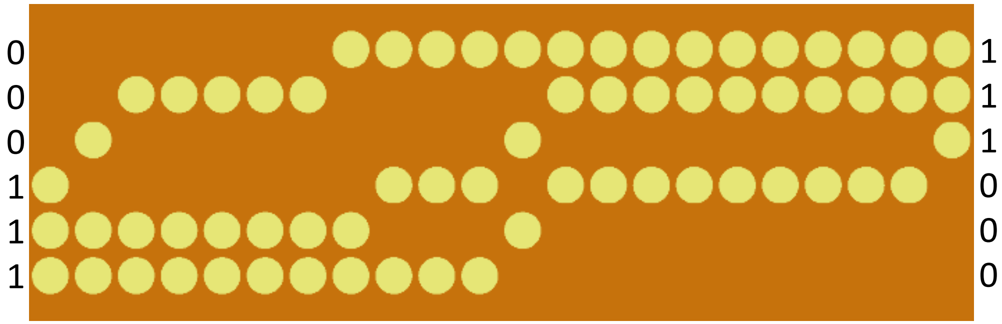


Randomization: "Lazy" sorting

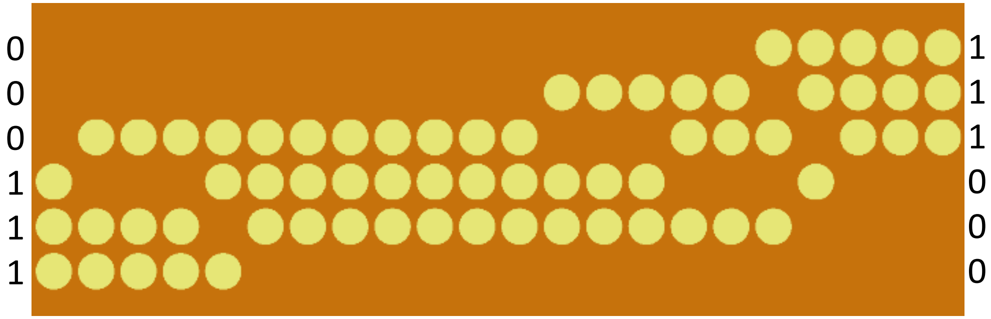
If 1 and 0 out of order, flip a coin to decide whether to swap them.

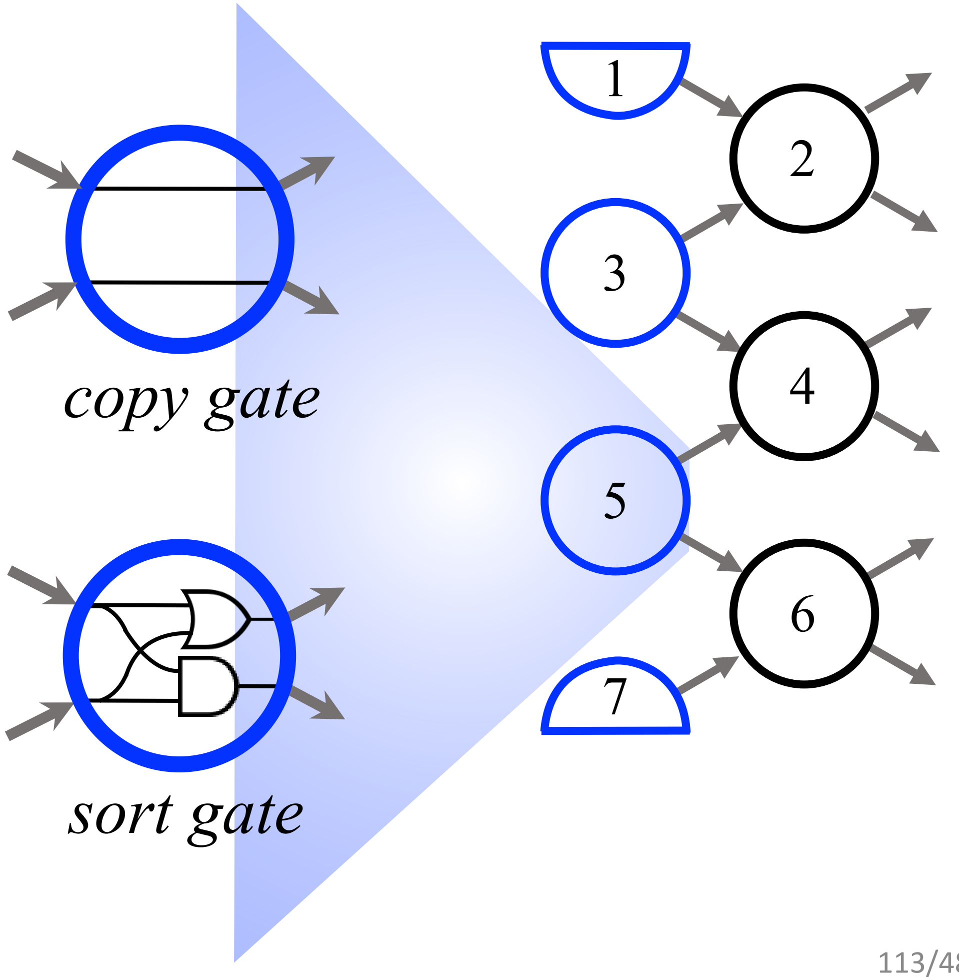


Randomization: “Lazy” sorting



If 1 and 0 out of order, flip a coin to decide whether to swap them.

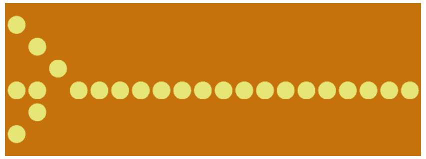




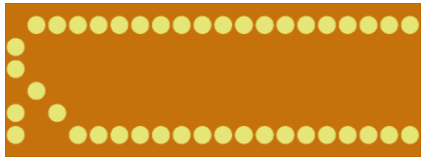
Deterministic circuits

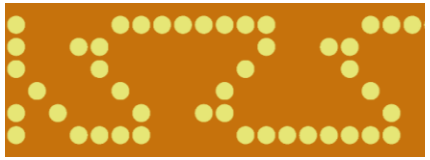
answer yes/no question

PARITY



MULTIPLEOF3

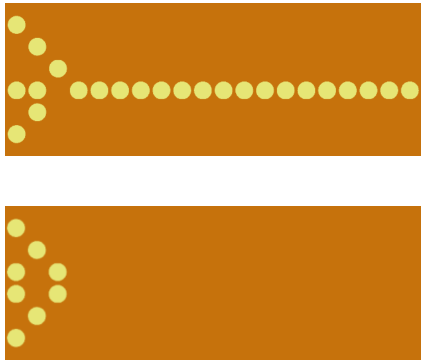




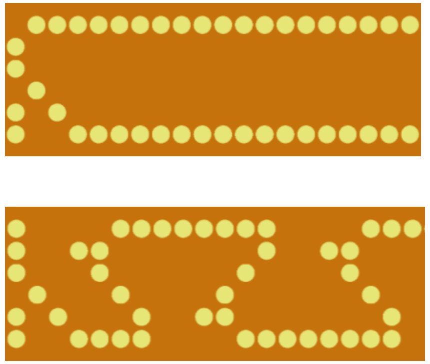
Deterministic circuits

answer yes/no question

PARITY



MULTIPLEOF3



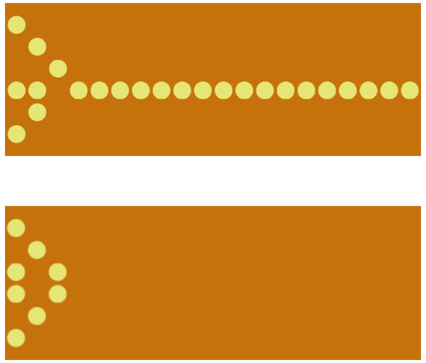
PALINDROME

yes

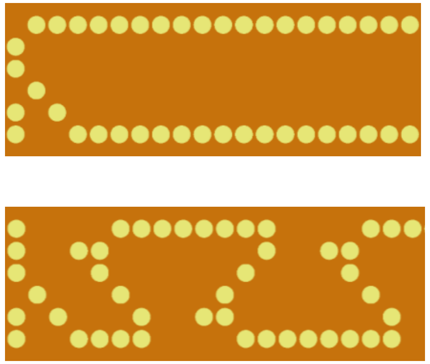
no

Deterministic circuits

PARITY

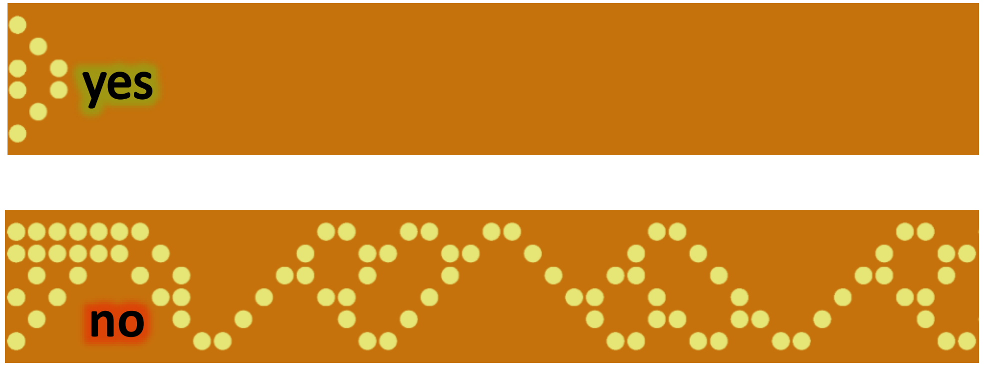


MULTIPLEOF3



PALINDROME

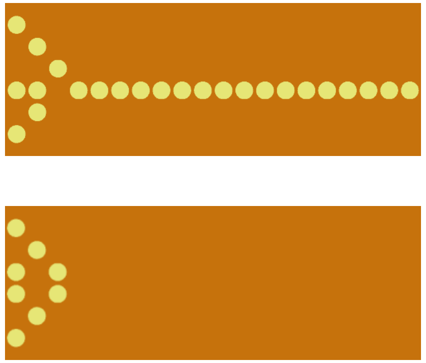
answer yes/no question



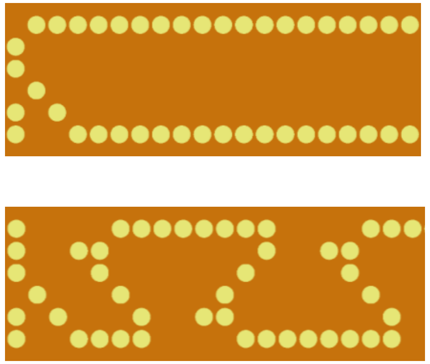
Deterministic circuits

answer yes/no question

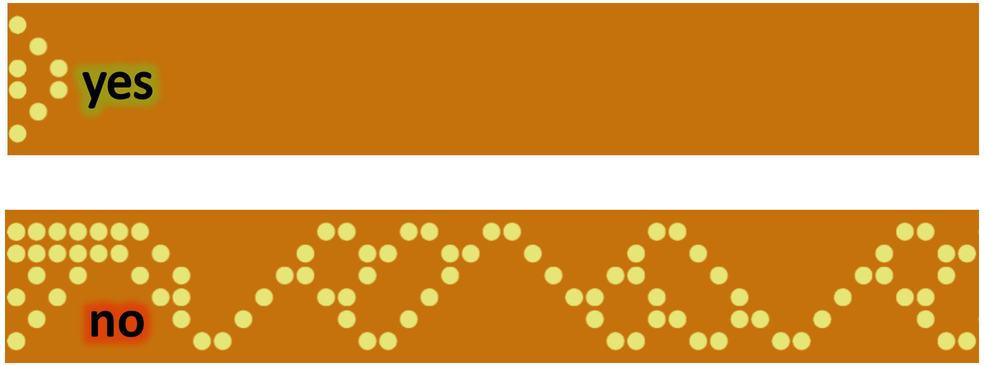
Parity



MultipleOf3

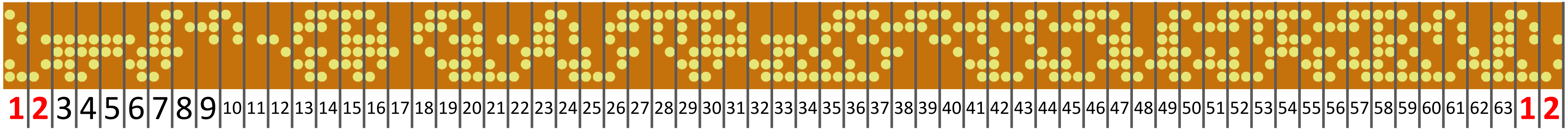


Palindrome



Cycle63

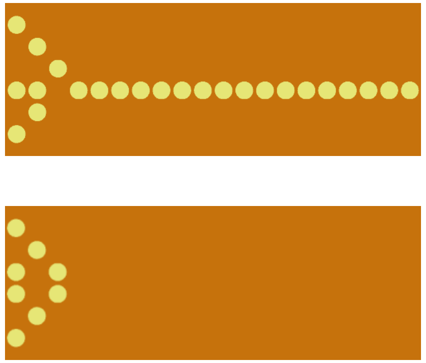
"count" as high as possible



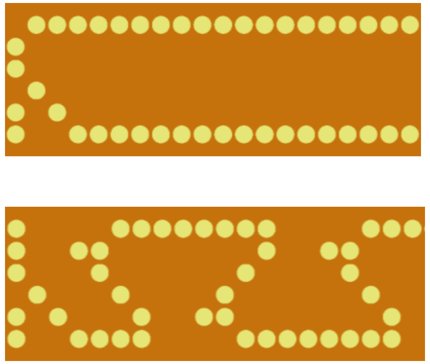
Deterministic circuits

answer yes/no question

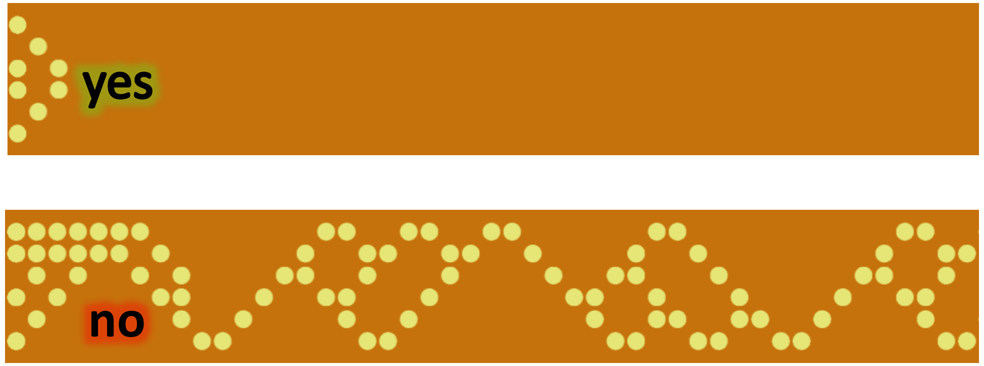
PARITY



MULTIPLEOF3

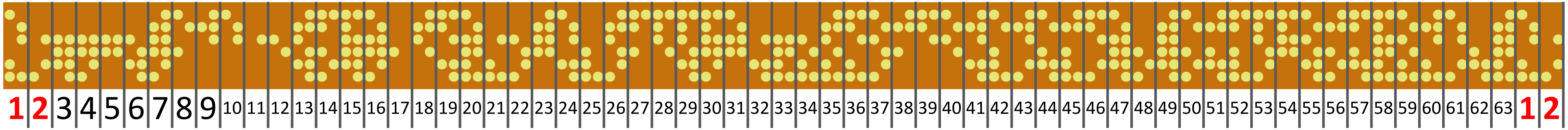


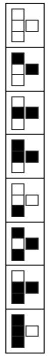
PALINDROME



CYCLE63

"count" as high as possible





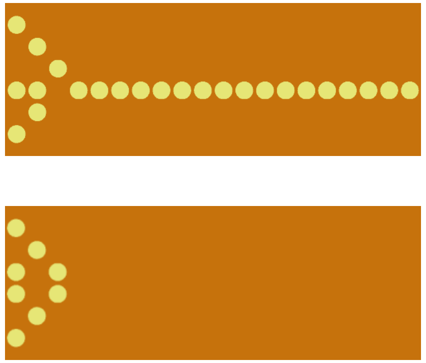
RULE110

simulate cellular automata

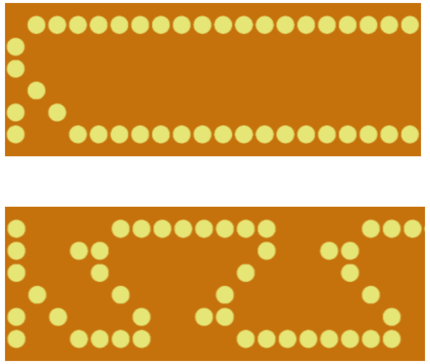
Deterministic circuits

answer yes/no question

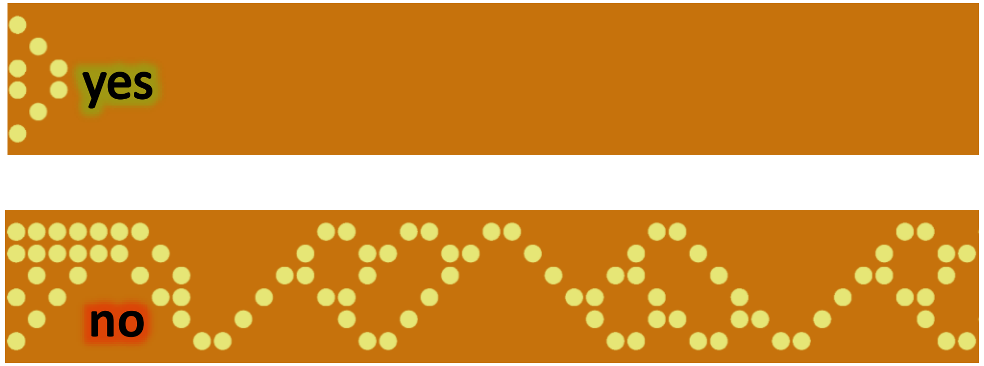
PARITY



MULTIPLEOF3

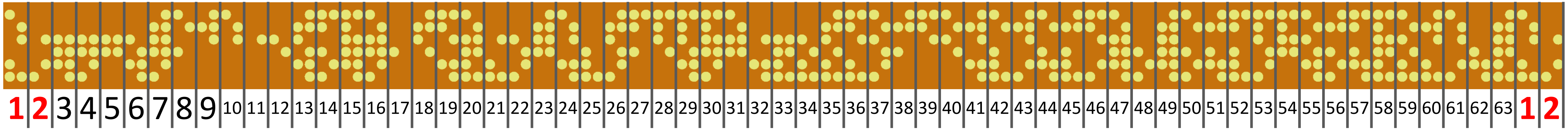


PALINDROME



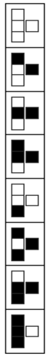
CYCLE63

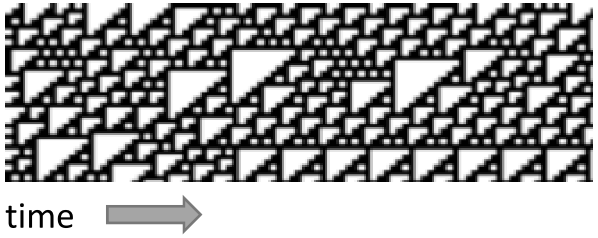
"count" as high as possible



RULE110

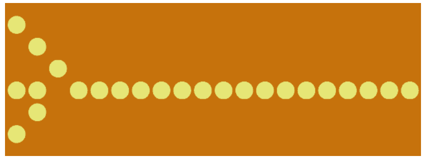
simulate cellular automata



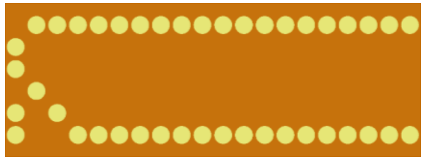


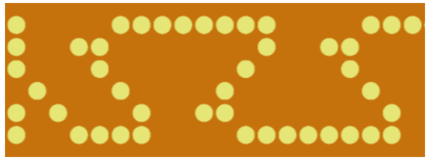
Deterministic circuits

PARITY



MULTIPLEOF3



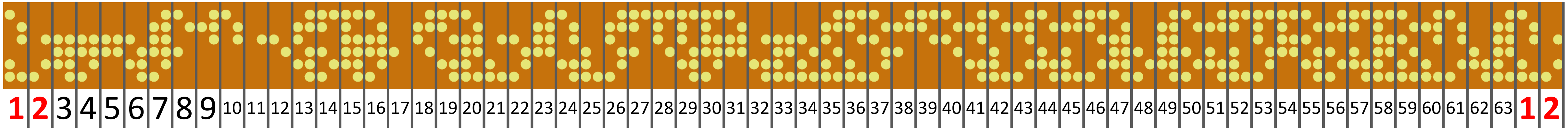


PALINDROME

answer yes/no question

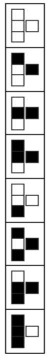
CYCLE63

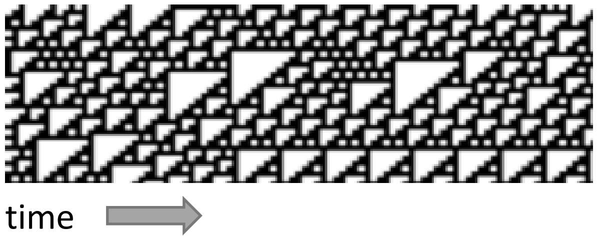
"count" as high as possible

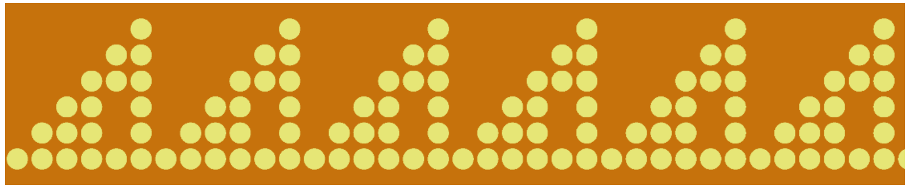


RULE110

simulate cellular automata







Theorem: Rule 110 can efficiently execute <u>any</u> algorithm.

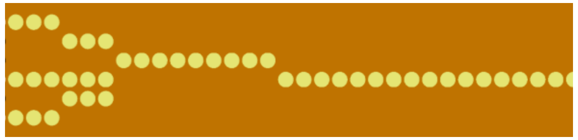
[Cook, <u>Complex Systems</u> 2004]
[Neary, Woods, <u>ICALP</u> 2006]

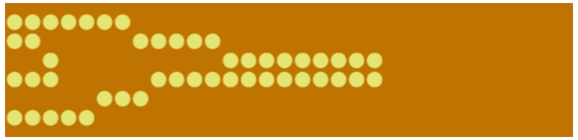
Randomized circuits

LAZYPARITY

Randomized circuits

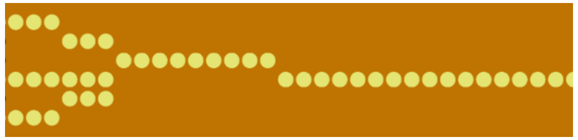
LAZYPARITY

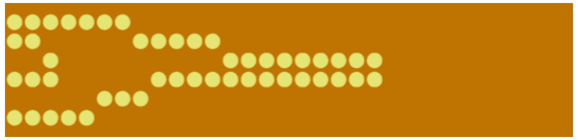




Randomized circuits

LazyParity

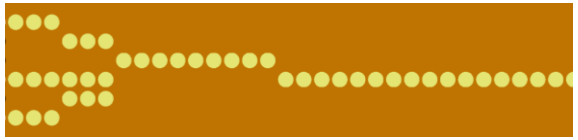


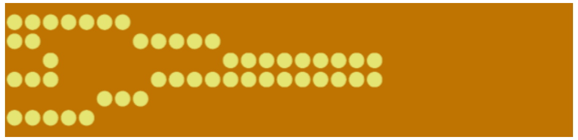


RandomWalkingBit

Randomized circuits

LazyParity



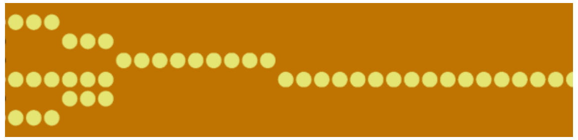


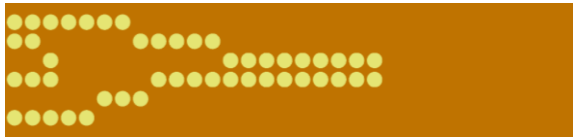
RandomWalkingBit

DiamondsAreForever

Randomized circuits

LazyParity





RandomWalkingBit

DiamondsAreForever

FairCoin

use biased coin to
simulate unbiased coin

Randomized circuits

LazyParity

RandomWalkingBit

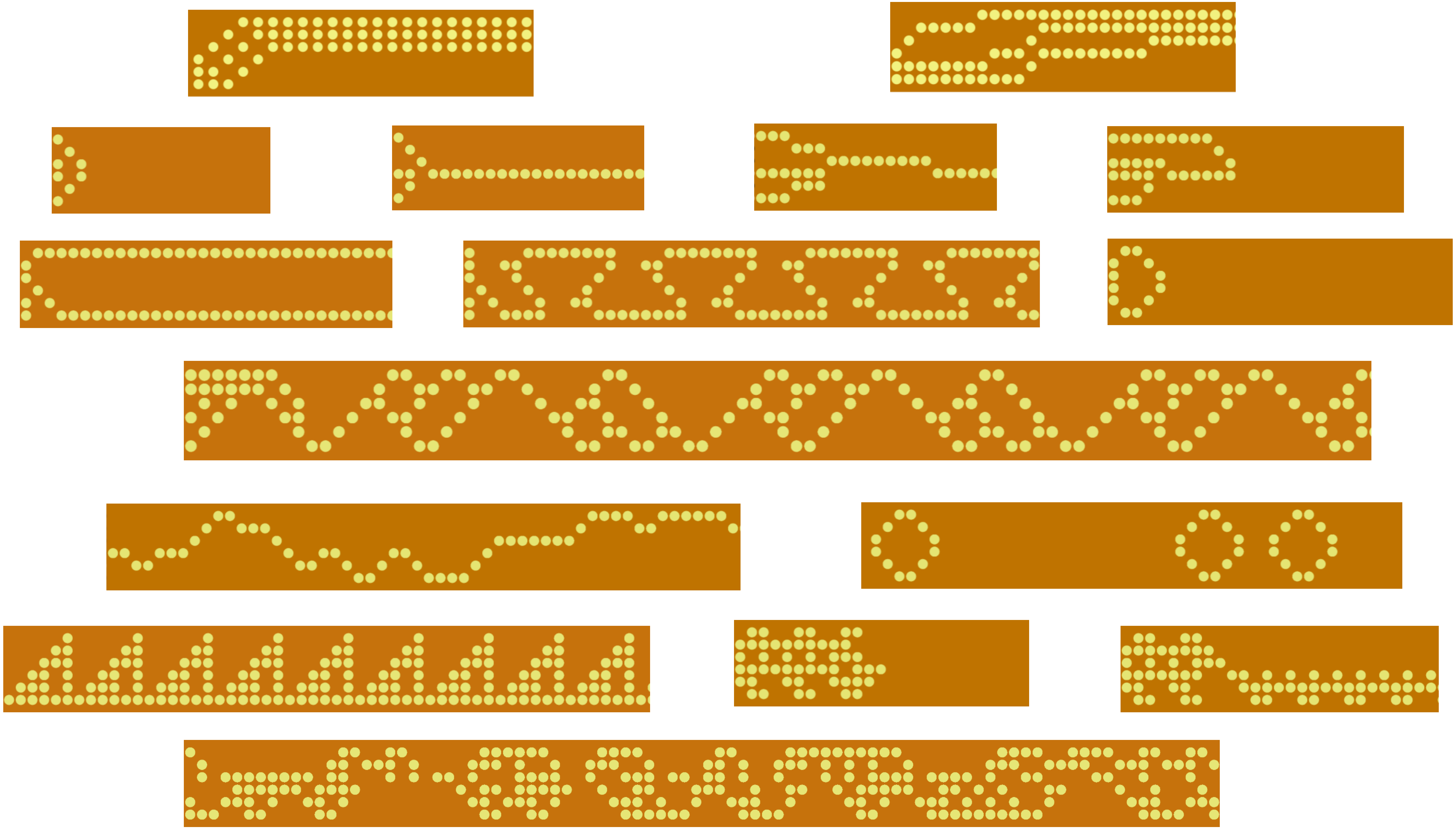
DiamondsAreForever

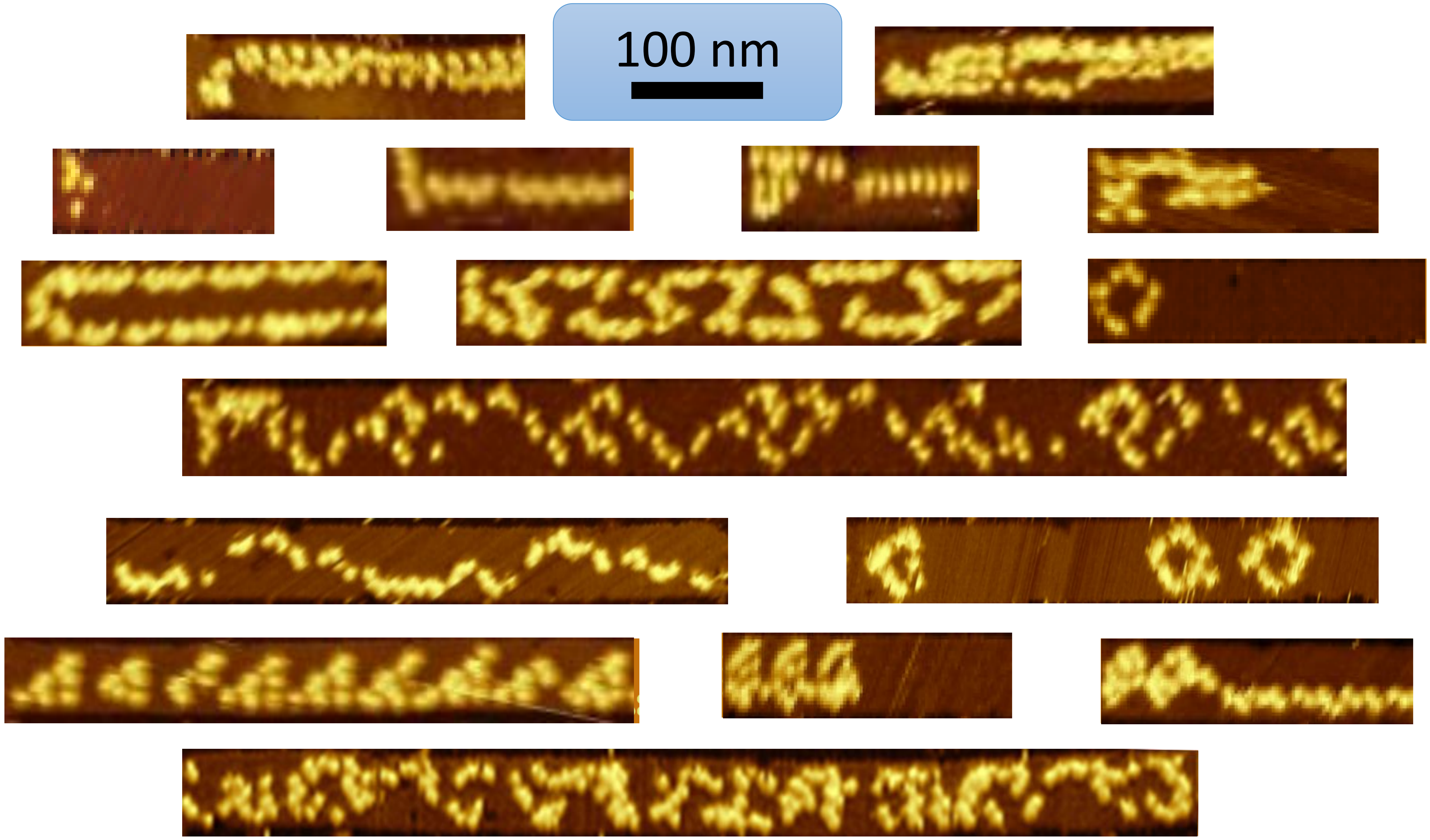
FairCoin

use biased coin to
simulate unbiased coin

Pr () = Pr () = ½

for **any** (positive) probabilities for the randomized gate

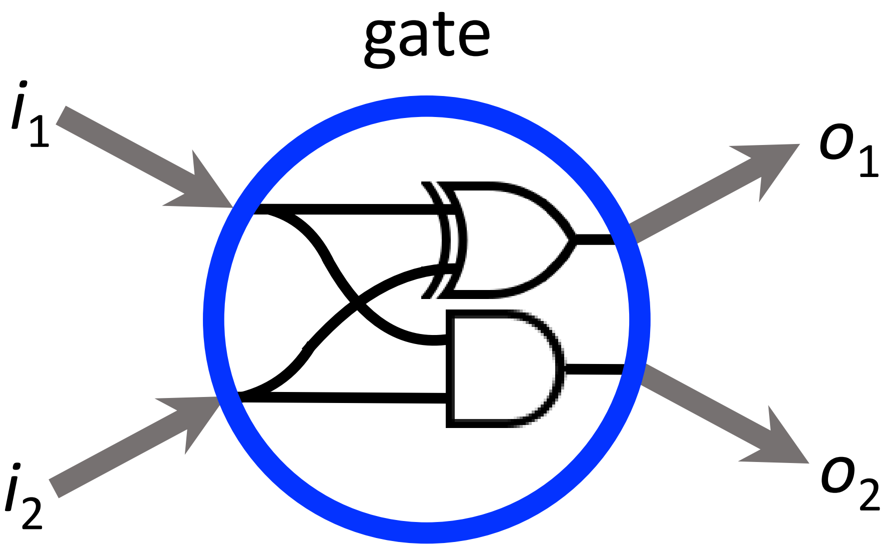



100 nm

Hierarchy of abstractions

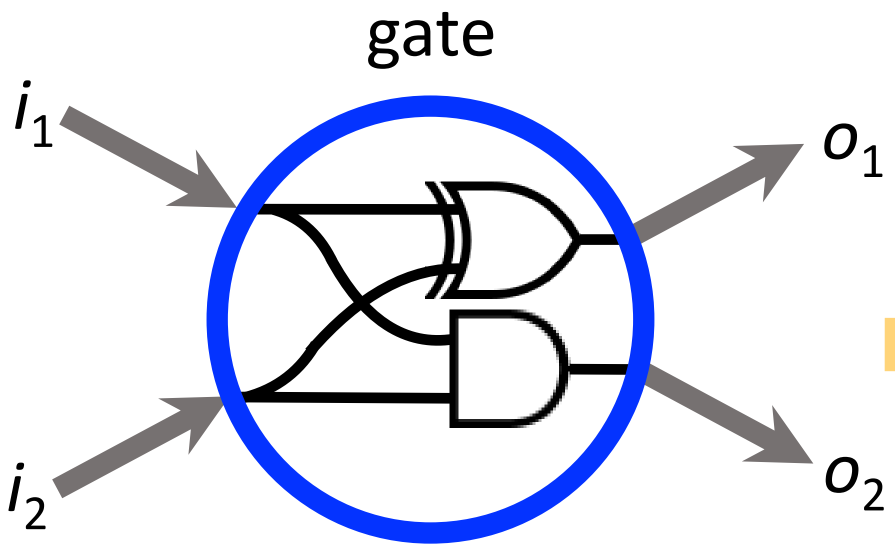
Bits:	Boolean circuits compute
Tiles:	**Tile growth implements circuits**
DNA:	DNA strands implement tiles

Gates → Tiles



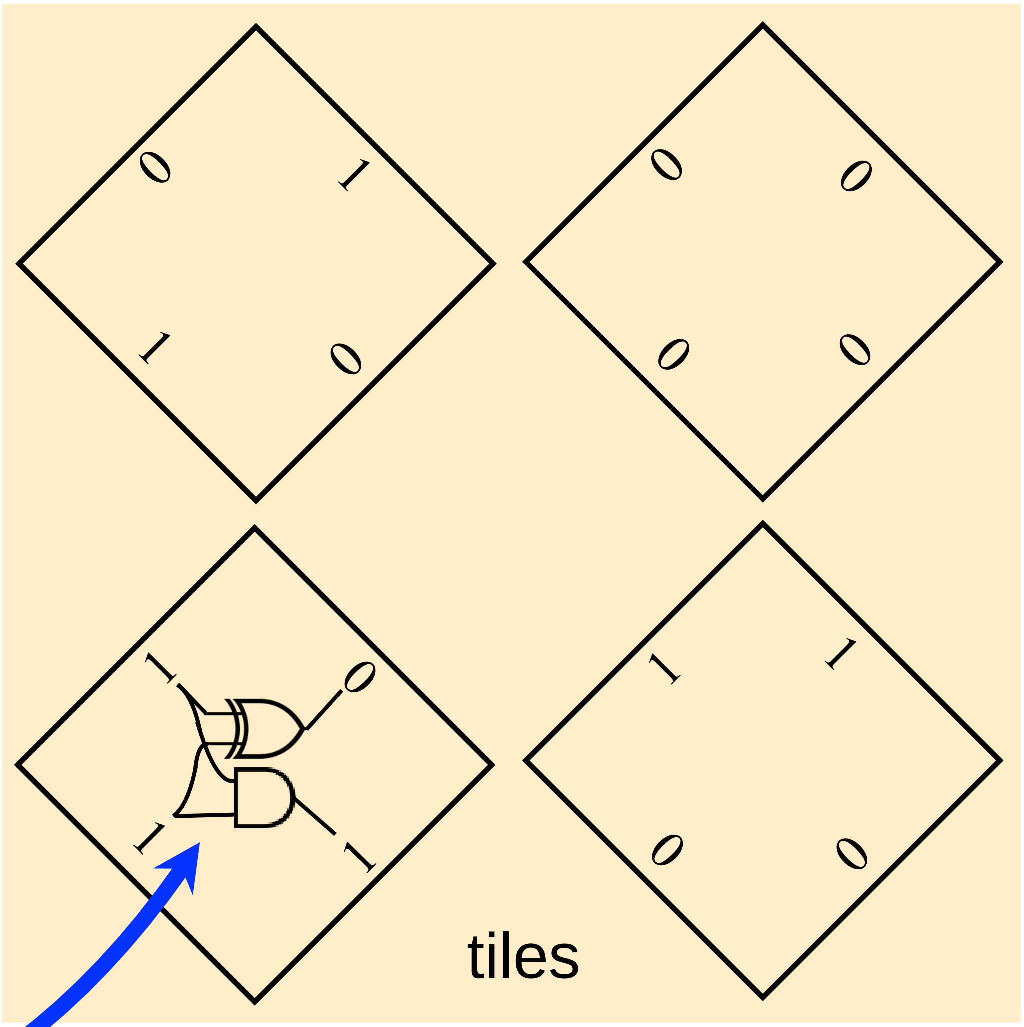
i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1

Gates → Tiles

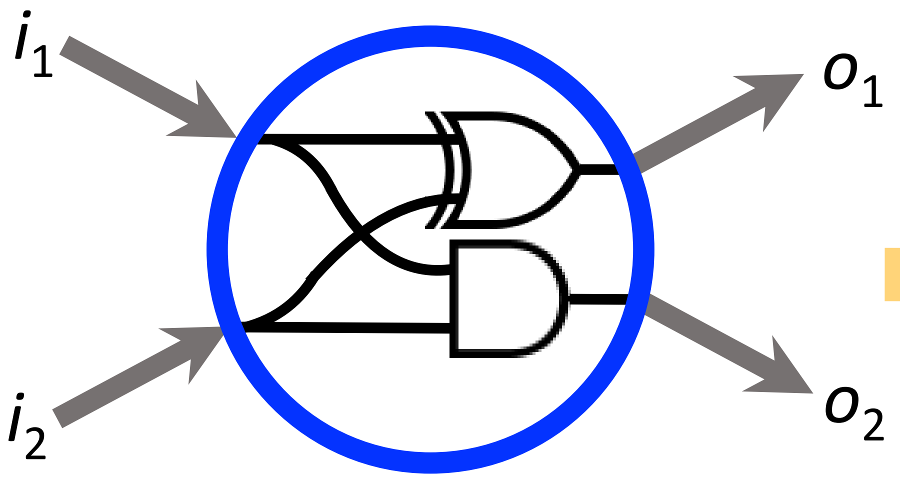


i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1

truth table row is encoded by a **tile** with 4 **glues** encoding bits

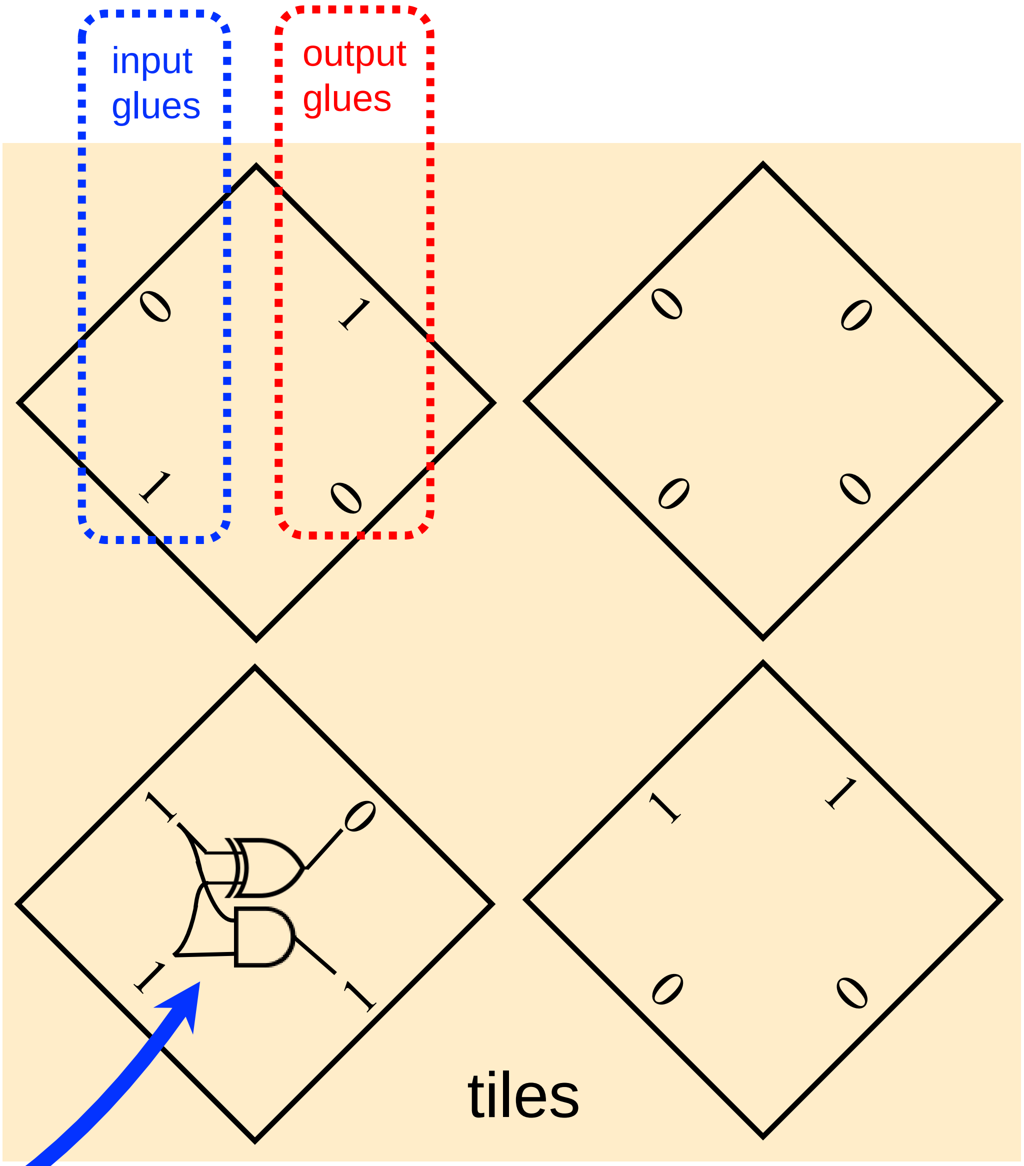


Gates → Tiles

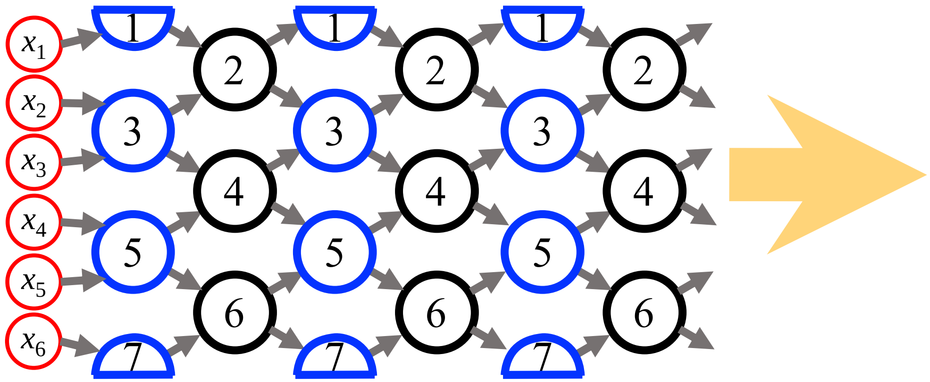


i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1

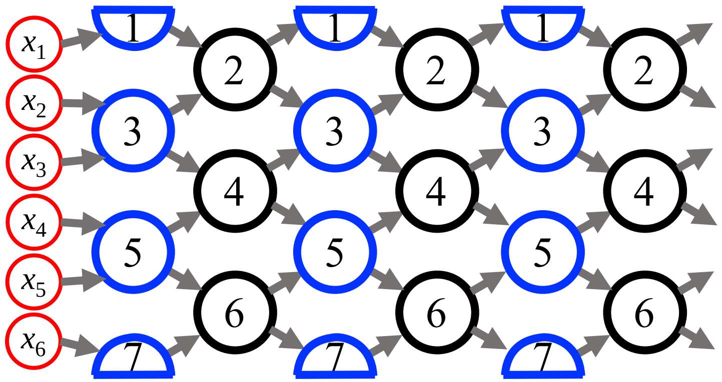
truth table row is
encoded by a **tile** with
4 **glues** encoding bits

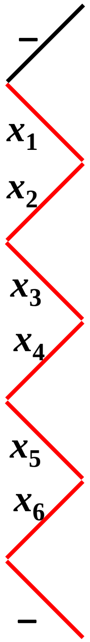


How tiles compute while growing (algorithmic self-assembly)

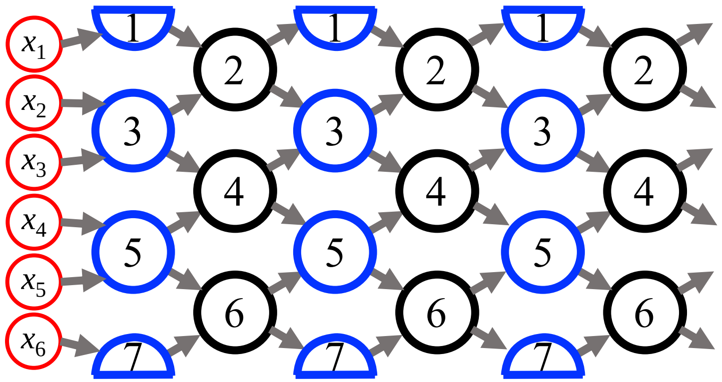


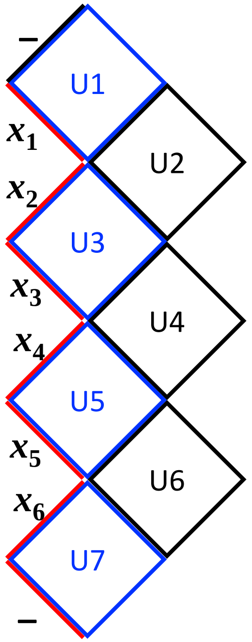
How tiles compute while growing (algorithmic self-assembly)



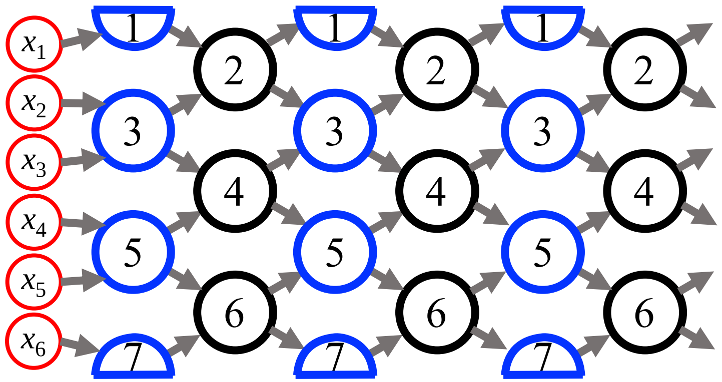


How tiles compute while growing (algorithmic self-assembly)

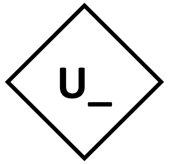


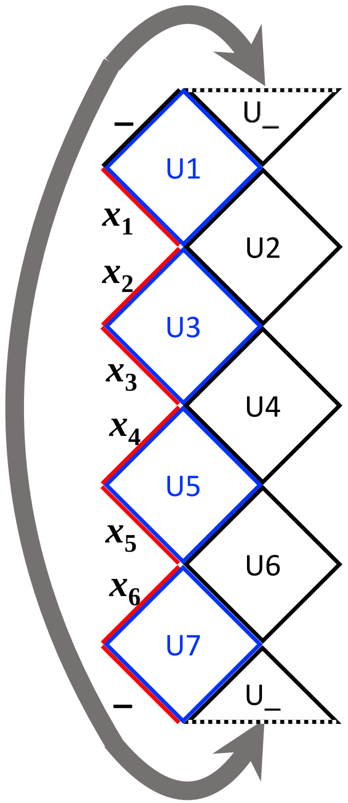


How tiles compute while growing (algorithmic self-assembly)

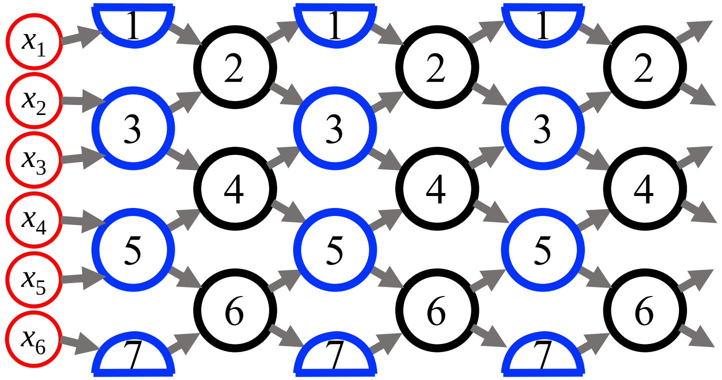


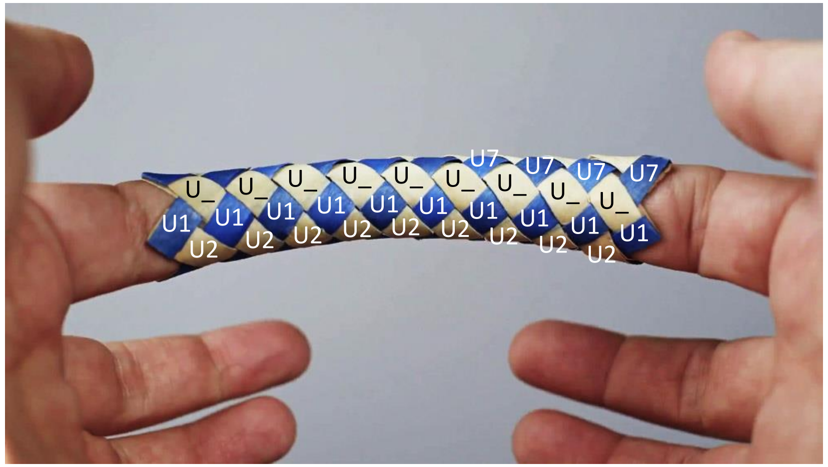
“data-free” tile wraps top to bottom to form a tube

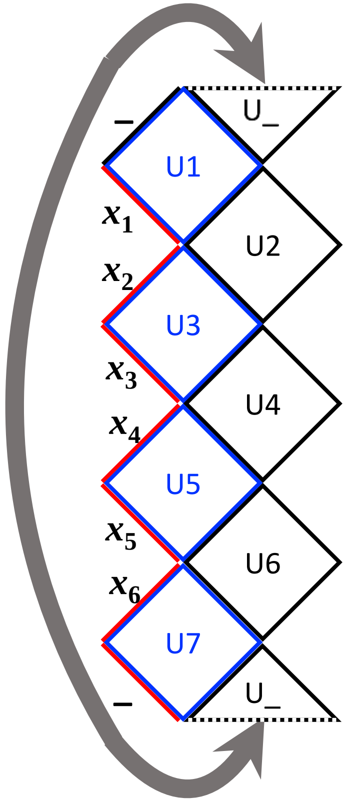




How tiles compute while growing (algorithmic self-assembly)







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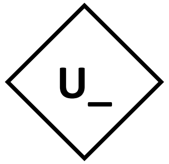

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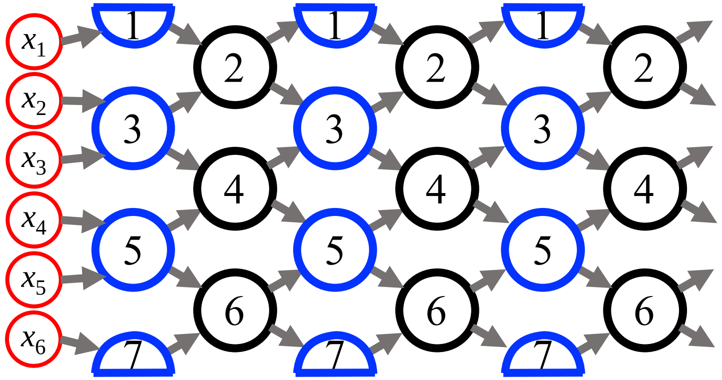
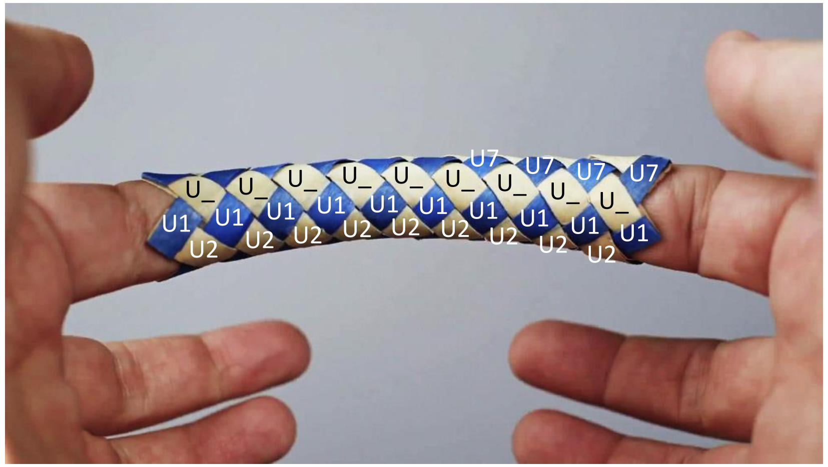
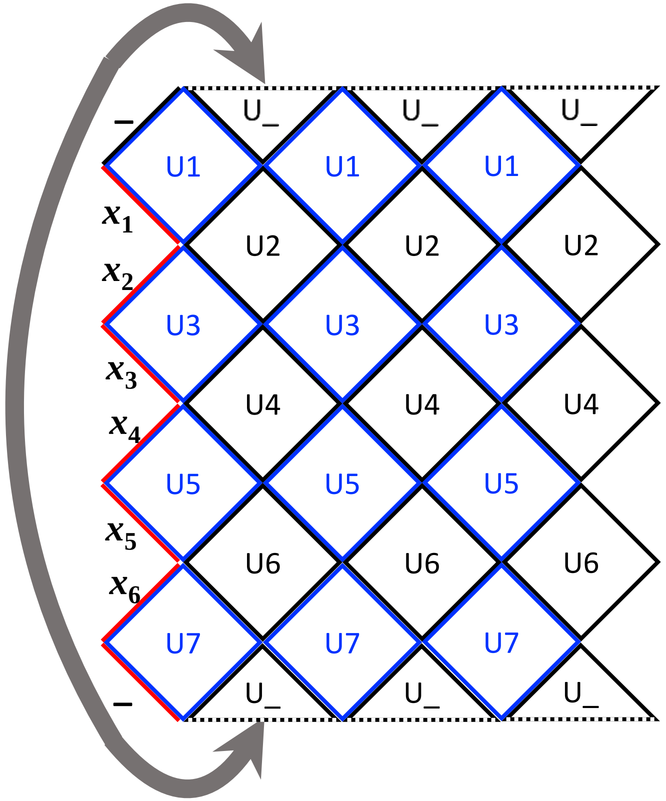


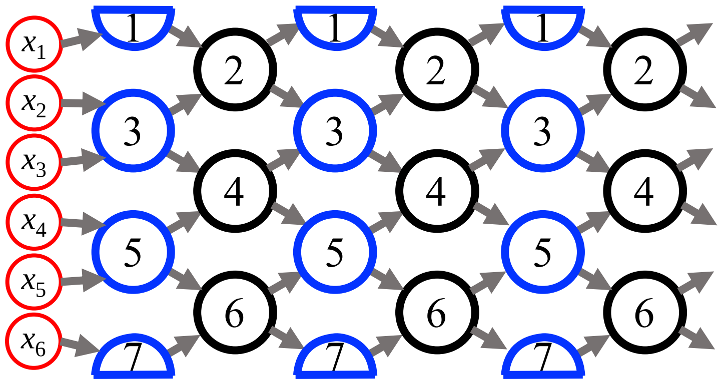


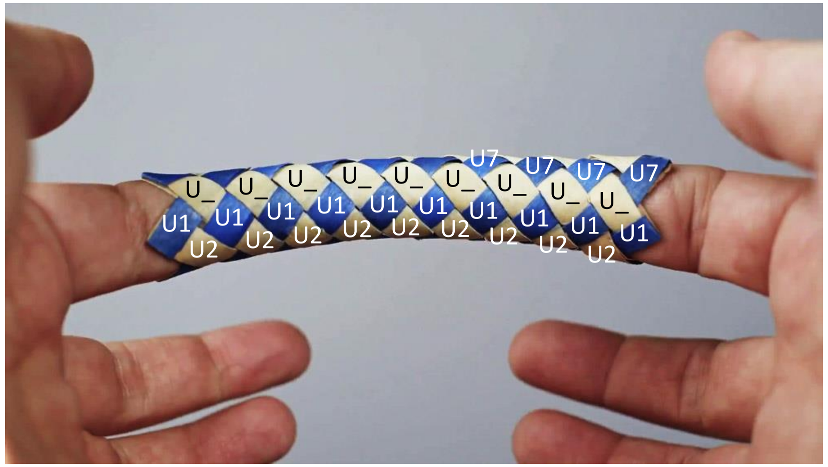
“data-free” tile wraps top to bottom to form a tube

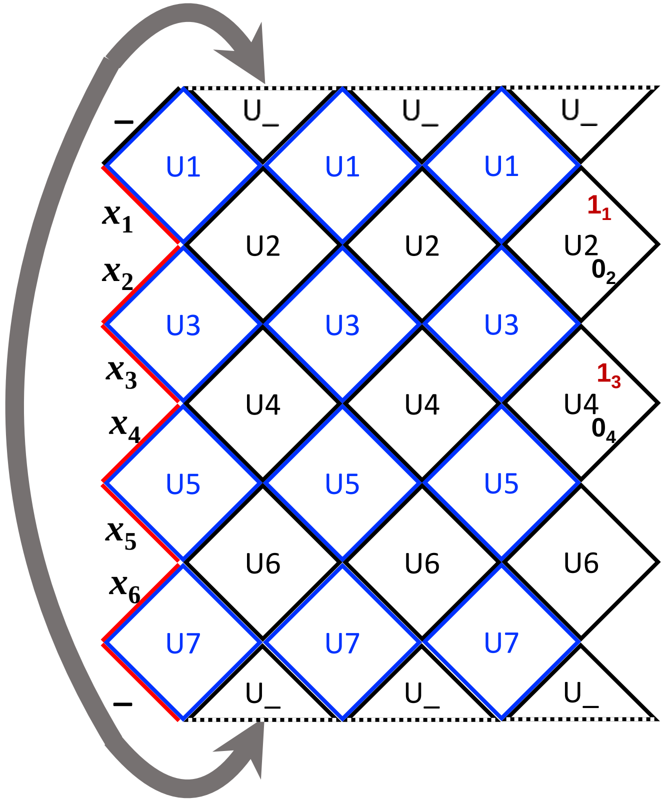
U_



How tiles compute while growing (algorithmic self-assembly)







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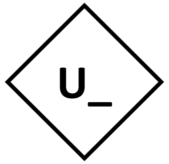

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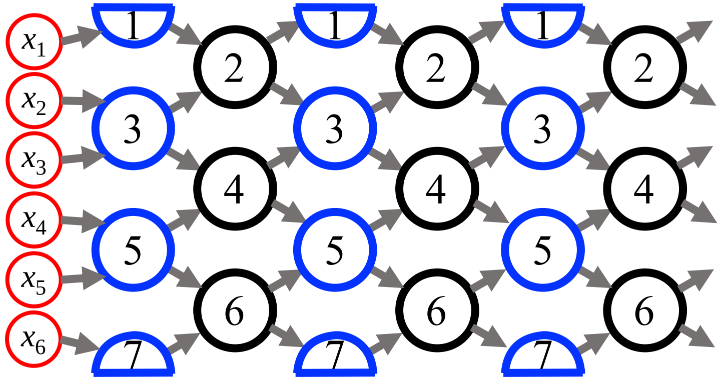
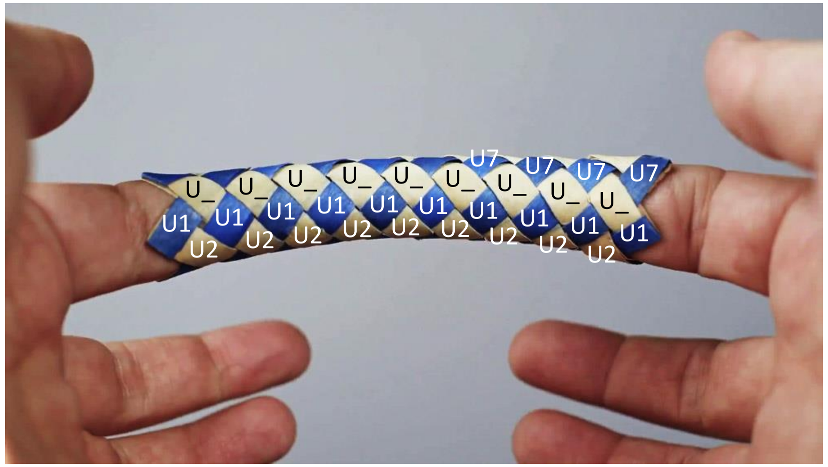
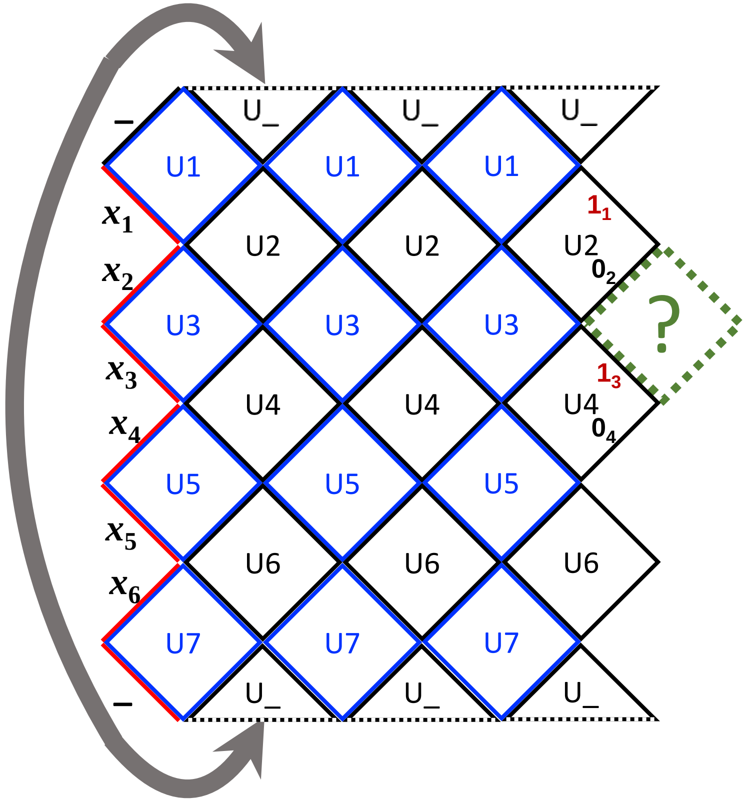
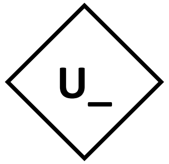


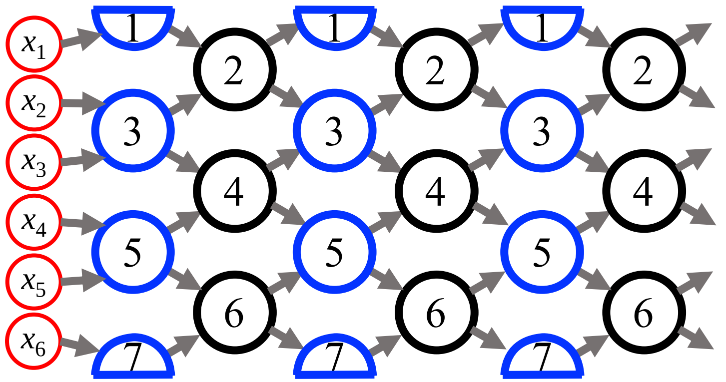


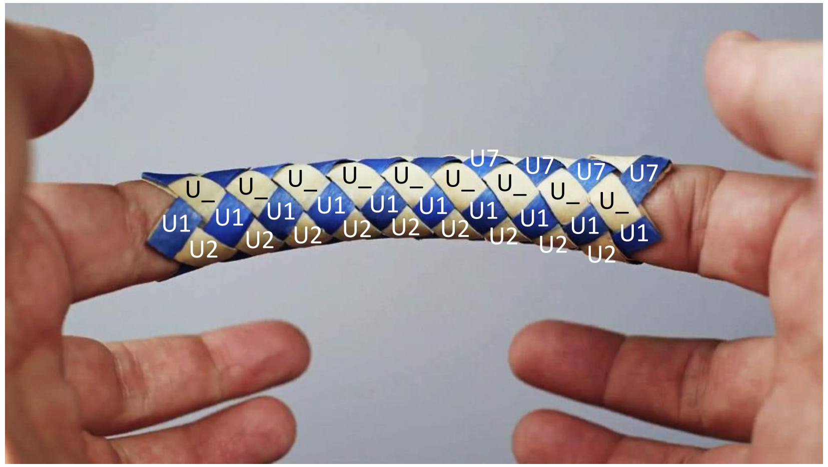


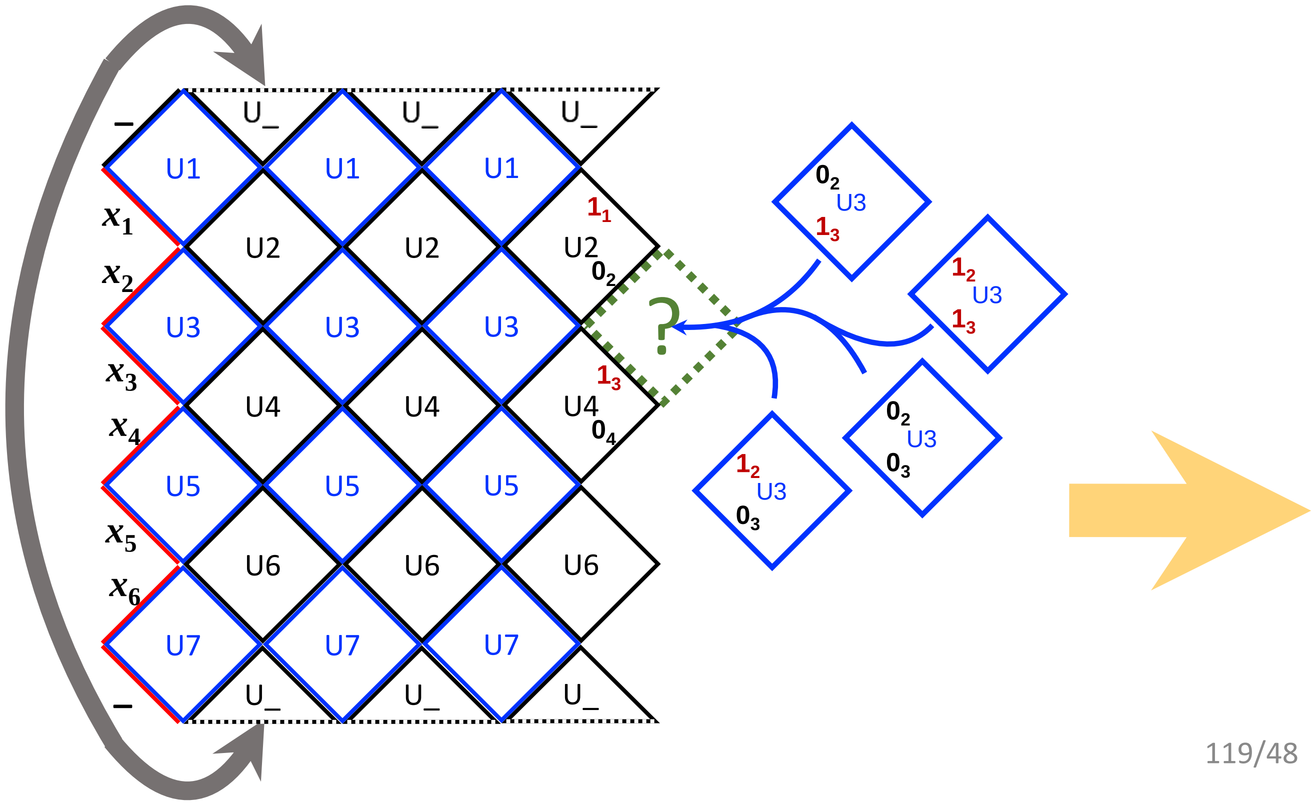
"data-free" tile wraps top to bottom to form a tube



How tiles compute while growing (algorithmic self-assembly)







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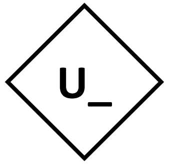

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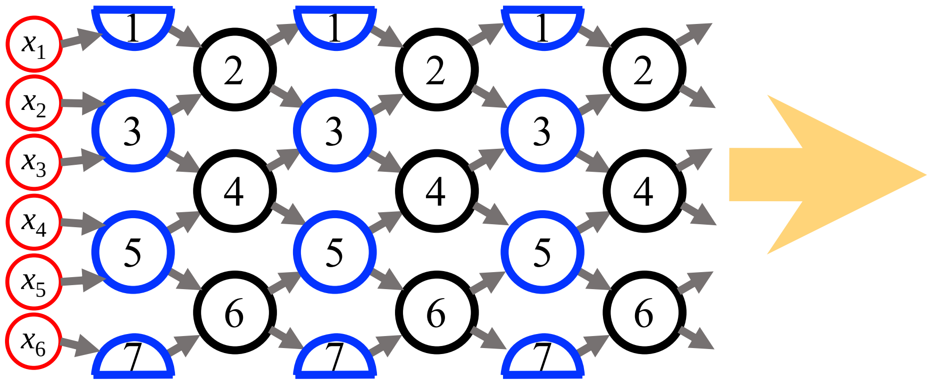

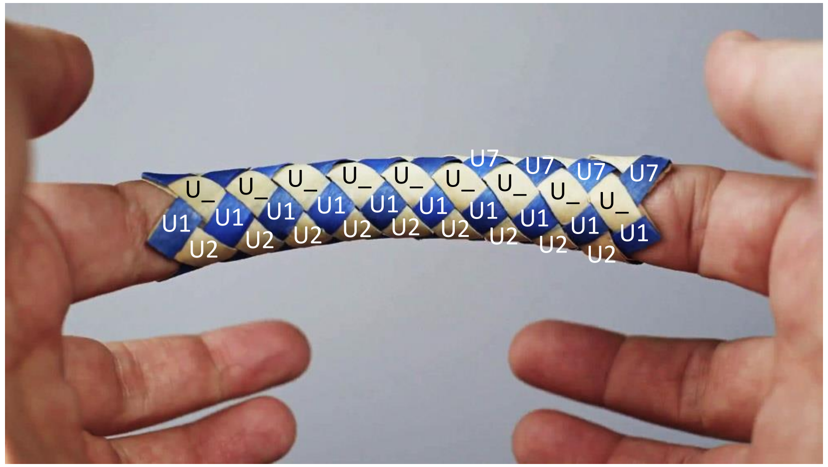

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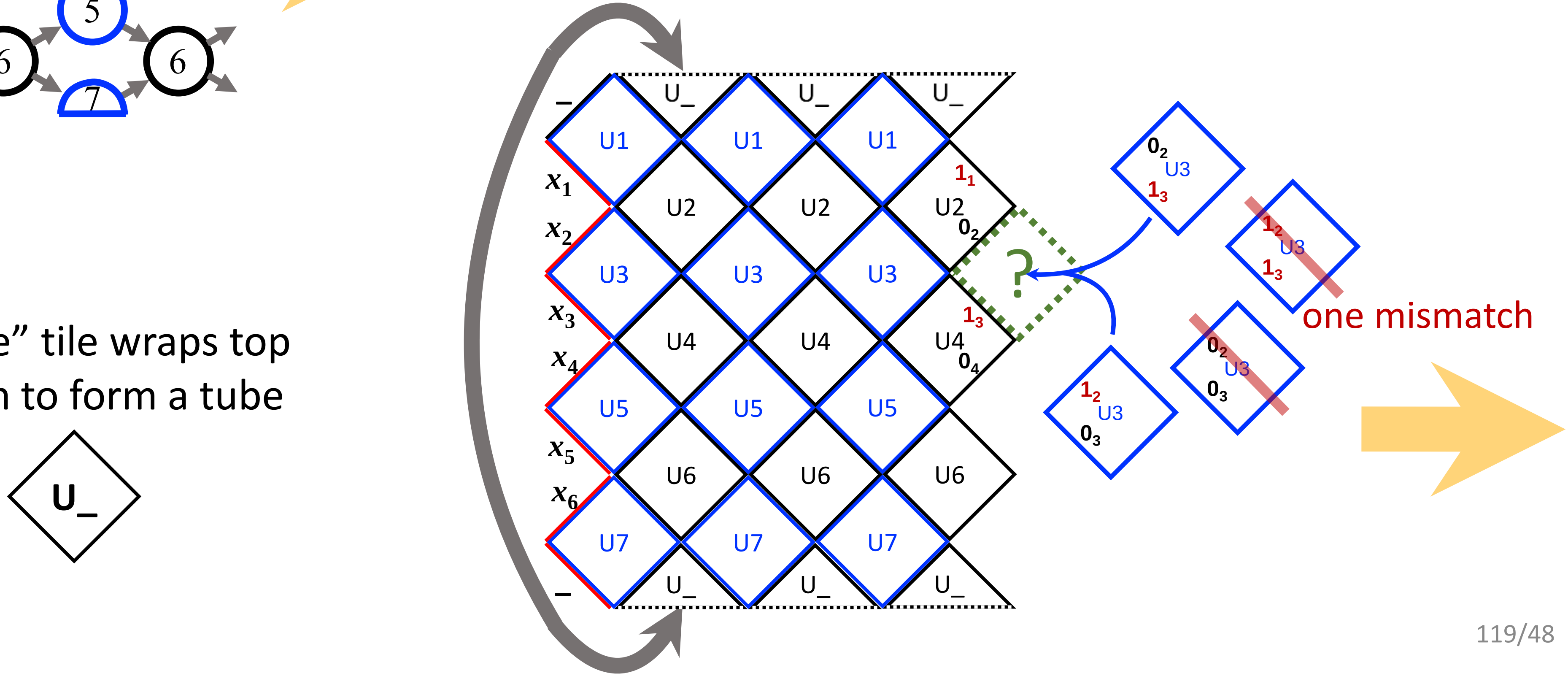
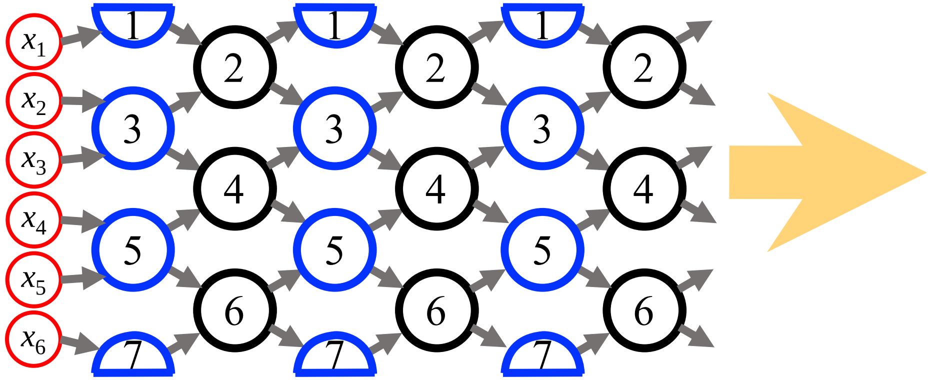
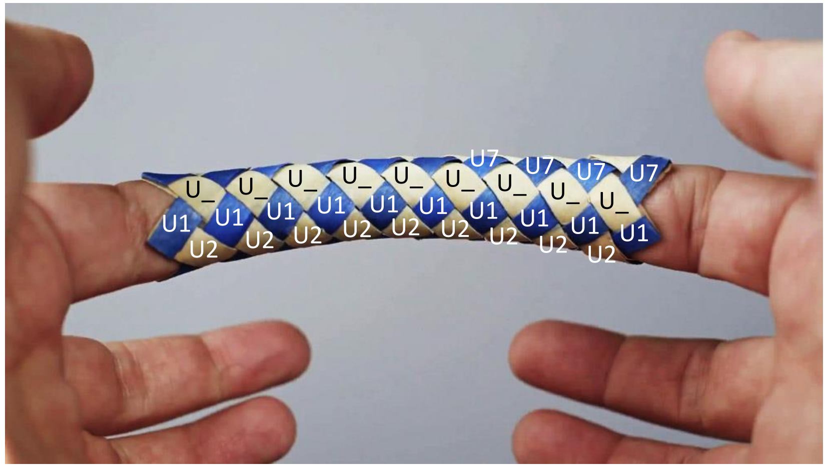
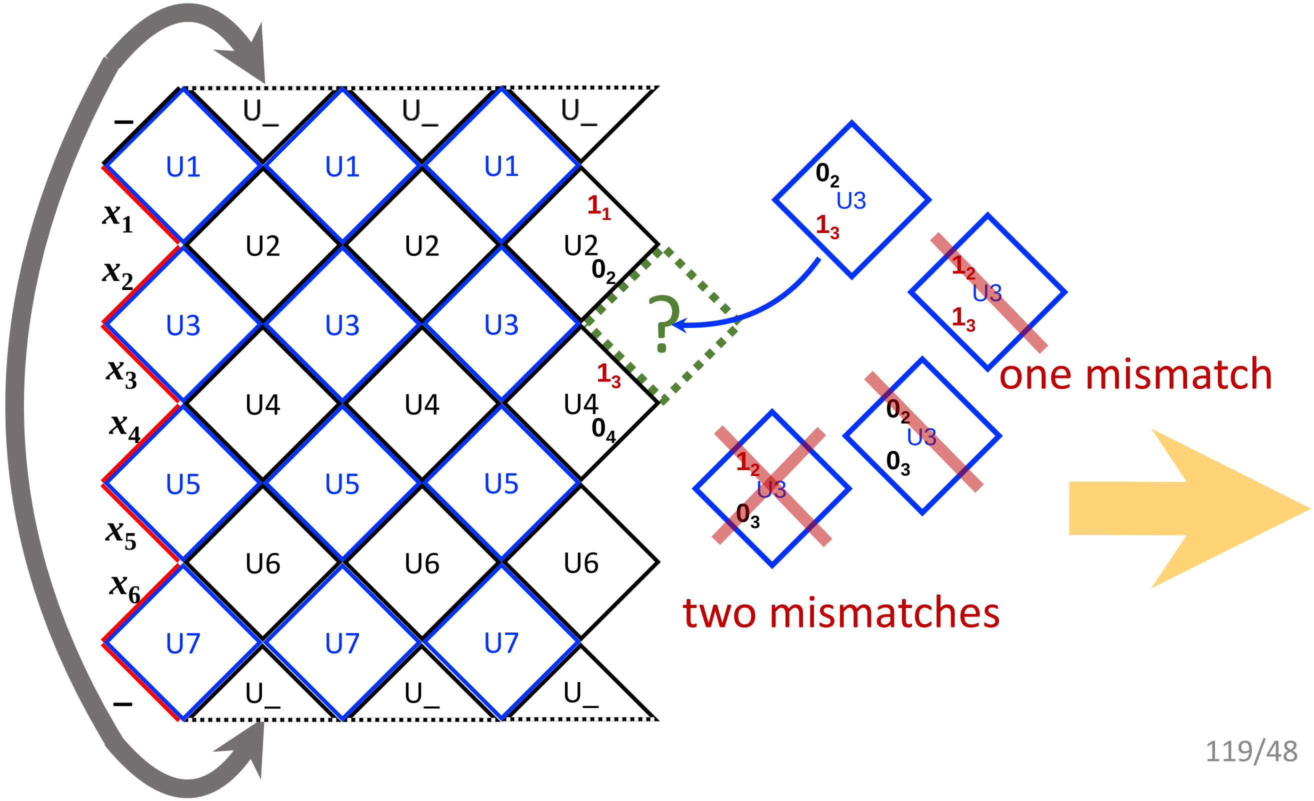


How tiles compute while growing (algorithmic self-assembly)







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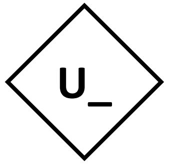
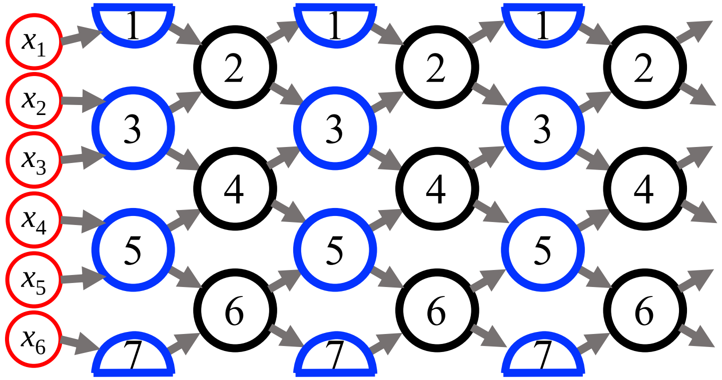
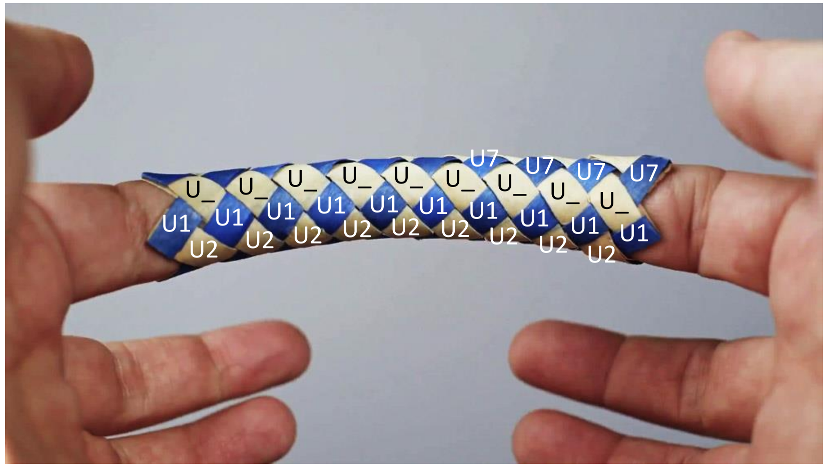
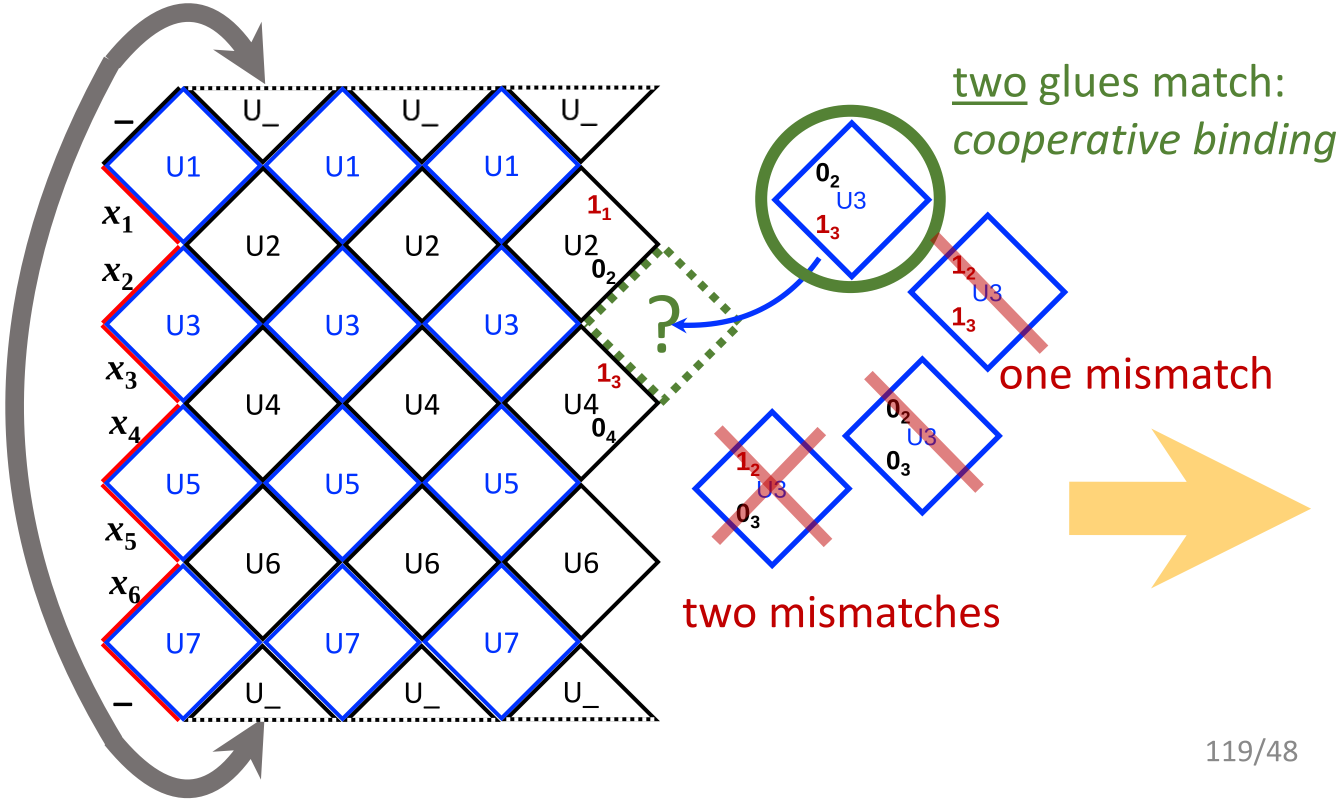


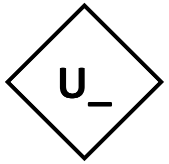
How tiles compute while growing (algorithmic self-assembly)



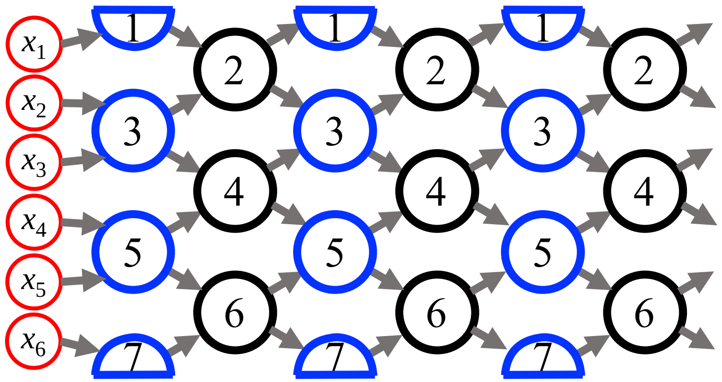


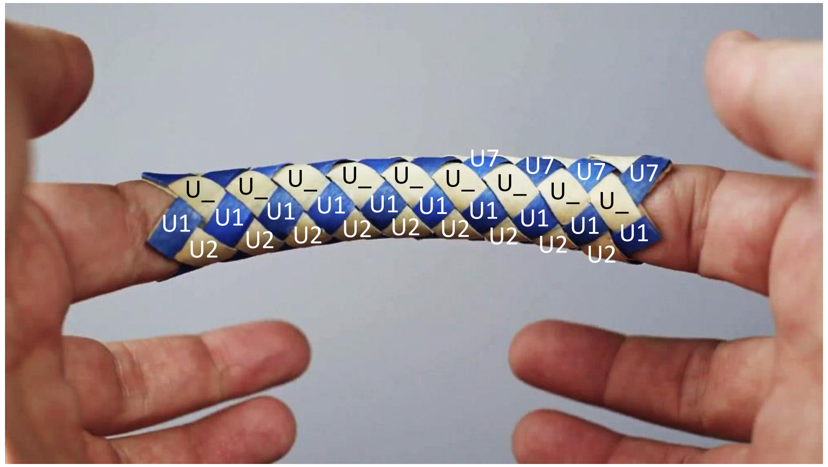


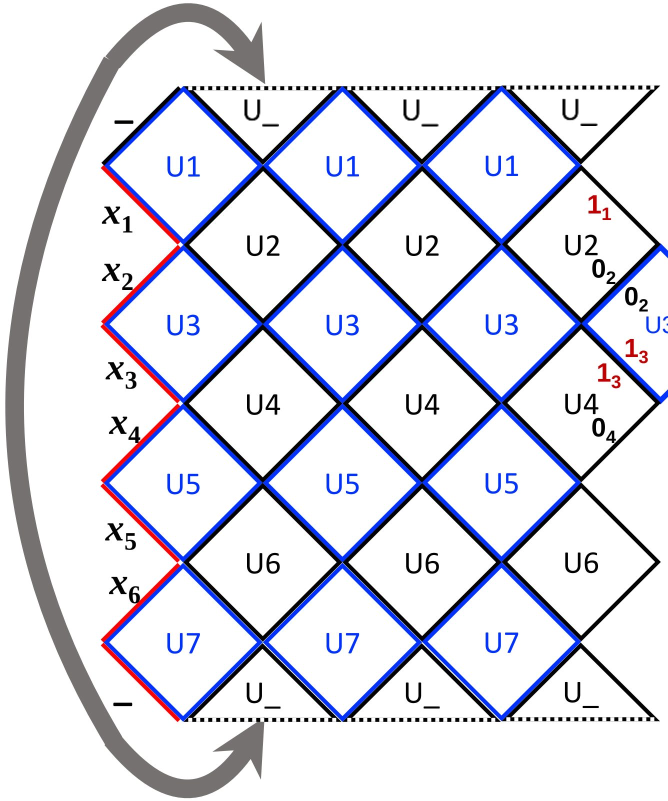
“data-free” tile wraps top to bottom to form a tube



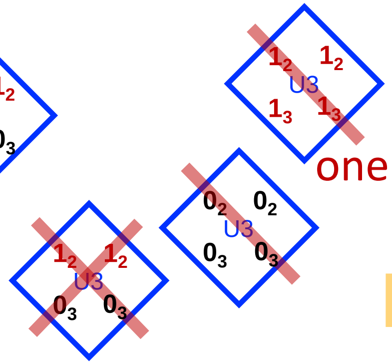
How tiles compute while growing (algorithmic self-assembly)







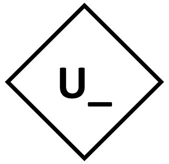
two glues match: *cooperative binding*



one mismatch

two mismatches

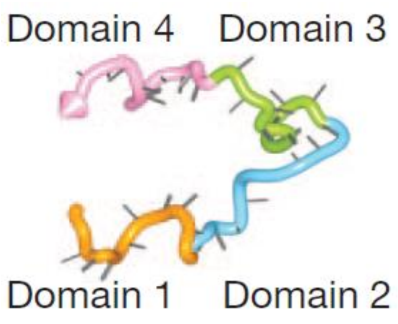
“data-free” tile wraps top to bottom to form a tube

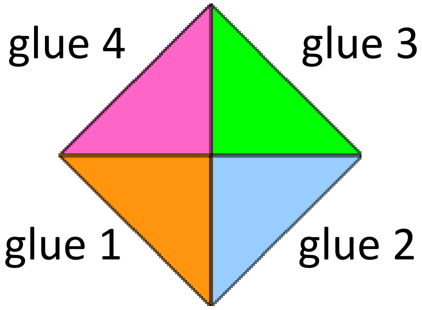


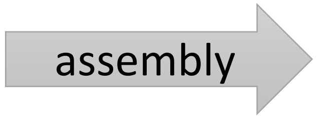
Hierarchy of abstractions

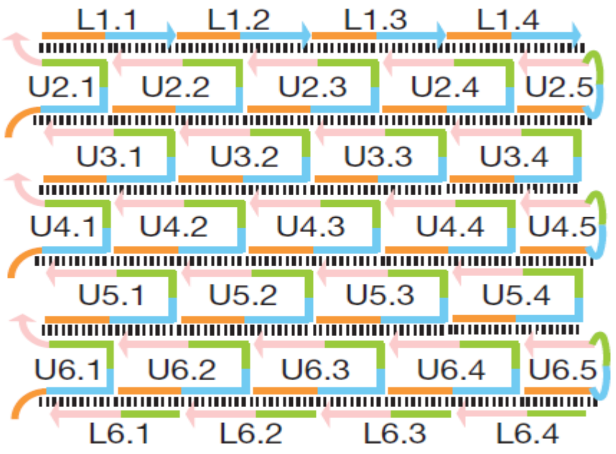
Bits:	Boolean circuits compute
Tiles:	Tile growth implements circuits
DNA:	**DNA strands implement tiles**

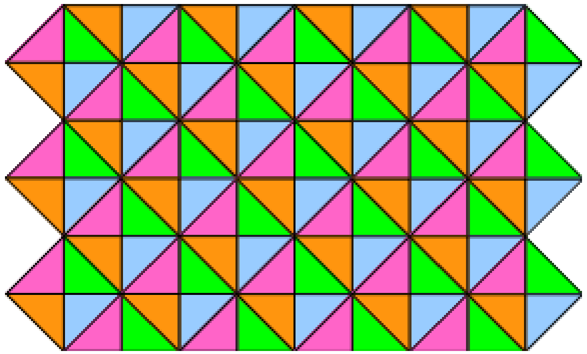
DNA single-stranded tiles





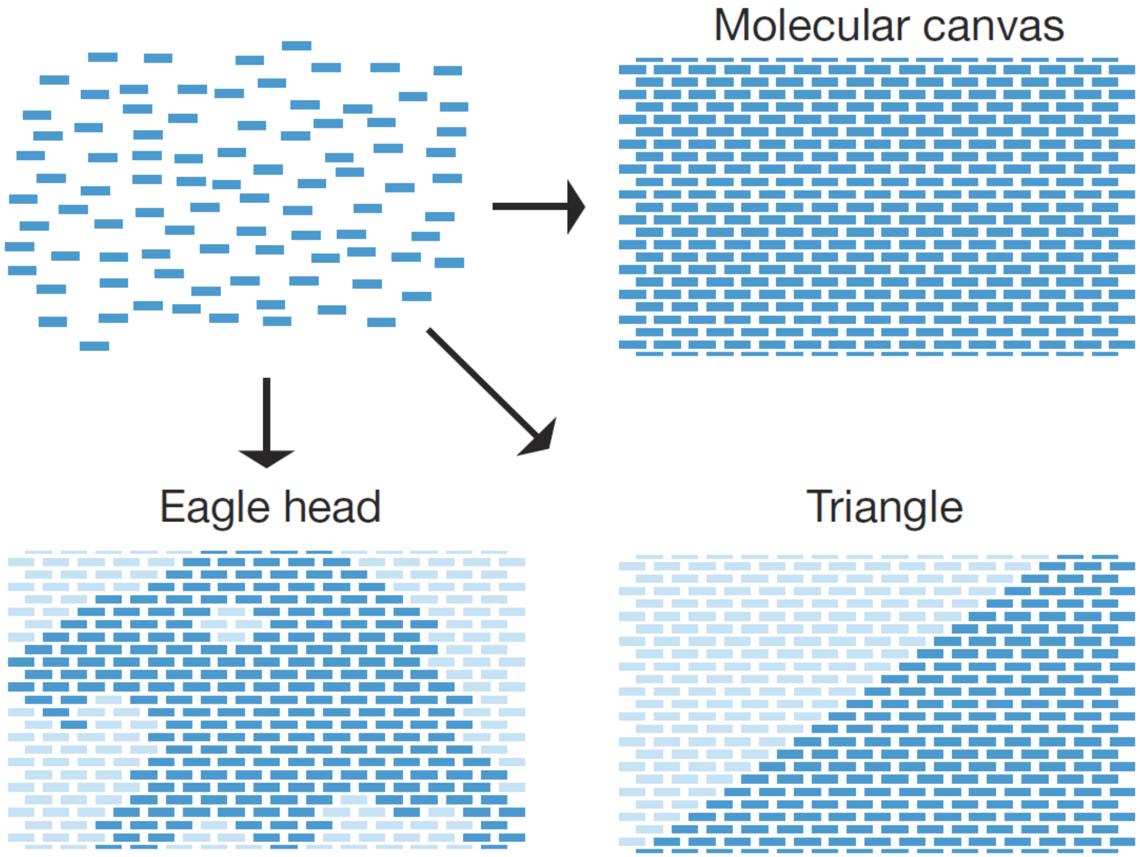






Yin, Hariadi, Sahu, Choi, Park, LaBean, and Reif.
Programming DNA tube circumferences.
Science 2008

Single-stranded tiles for making any shape



Bryan Wei, Mingjie Dai, and Peng Yin.
Complex shapes self-assembled from single-stranded DNA tiles.
Nature 2012.

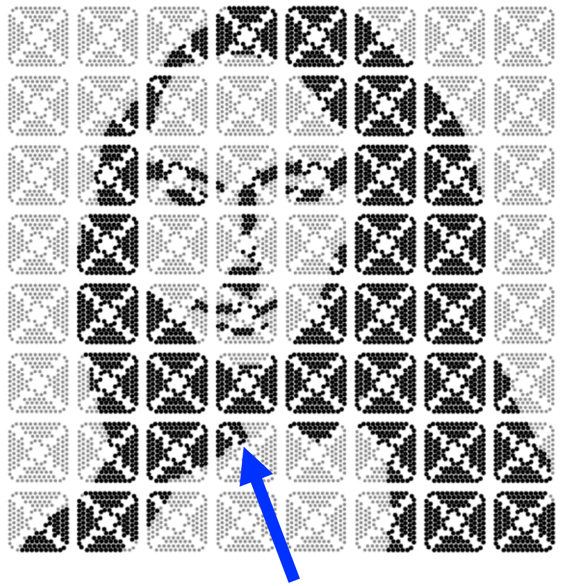
Uniquely addressed self-assembly versus algorithmic

Unique addressing: each DNA “monomer” appears **exactly once** in final structure.

single DNA origami

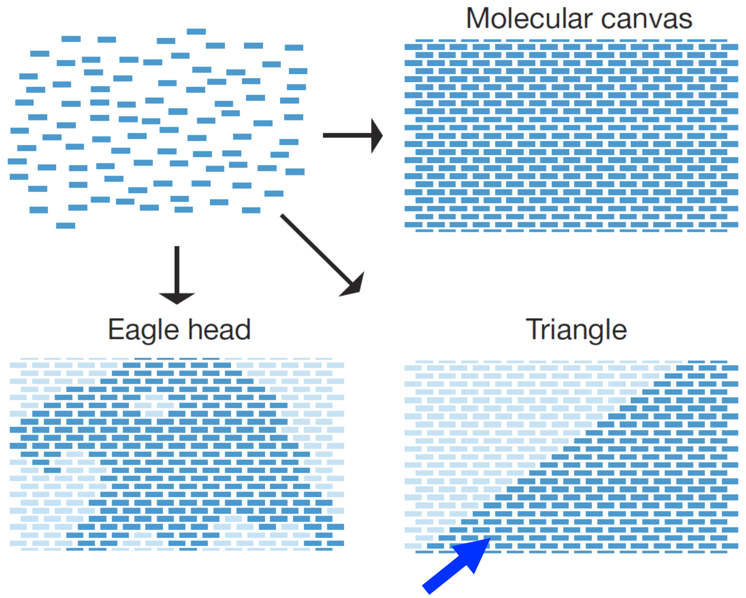
staple strand for position (4,2)

array of many DNA origamis



origami for position (4,2)

uniquely-addressed tiles



tile for position (4,2)

Uniquely addressed self-assembly versus algorithmic

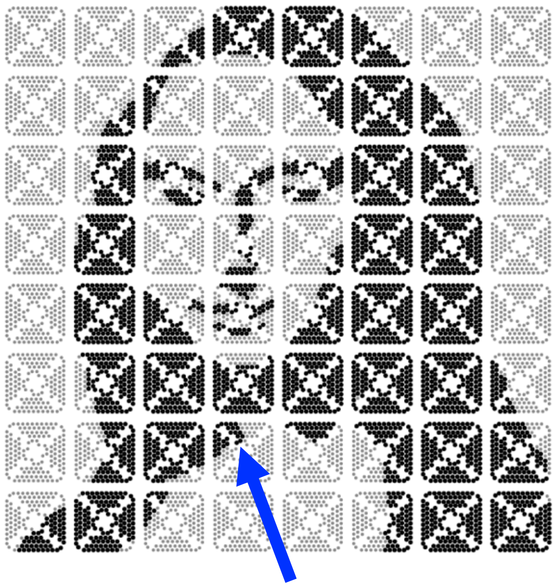
Unique addressing: each DNA “monomer” appears **exactly once** in final structure.

Algorithmic: DNA tiles are **reused** throughout the structure.

single DNA origami

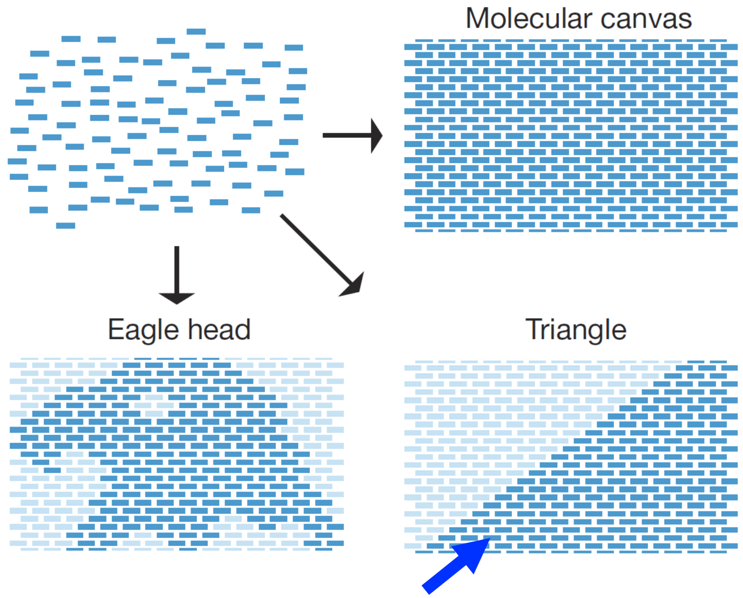
staple strand for position (4,2)

array of many DNA origamis



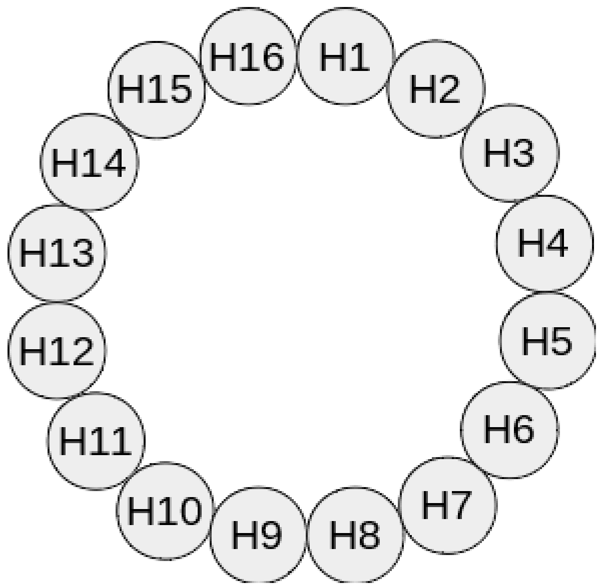
origami for position (4,2)

uniquely-addressed tiles

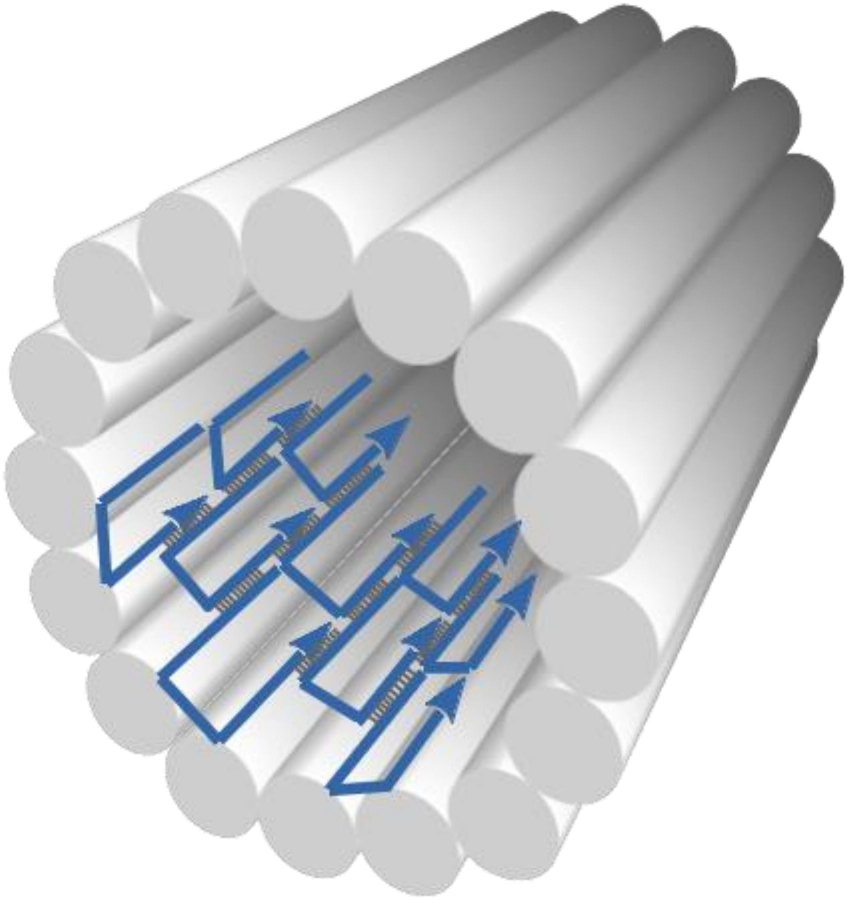


tile for position (4,2)

Single-stranded tile tubes

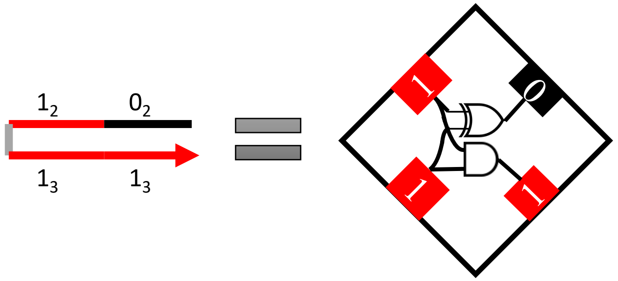


DNA-level diagram of 20-helix tube

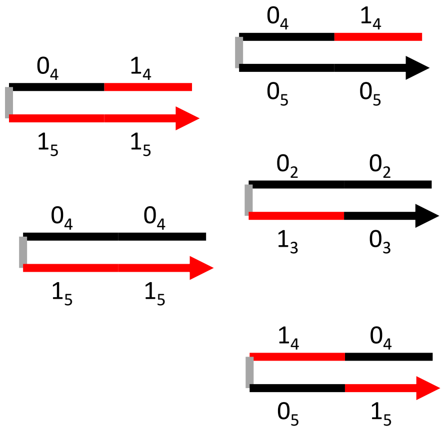


Yin, Hariadi, Sahu, Choi, Park, LaBean, and Reif. *Programming DNA tube circumferences*, Science 2008.

Seeded growth

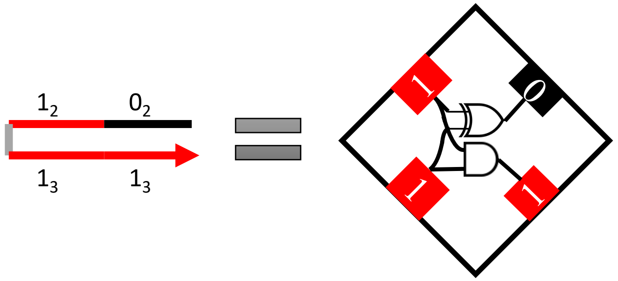


single-stranded tiles
implementing circuit gates

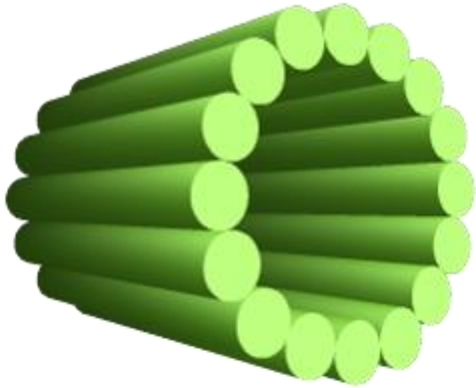


need barrier to <u>nucleation</u>
(tile growth without seed);
[tile]=100 nM;
temperature=50.9° C

Seeded growth



DNA origami seed



single-stranded tiles
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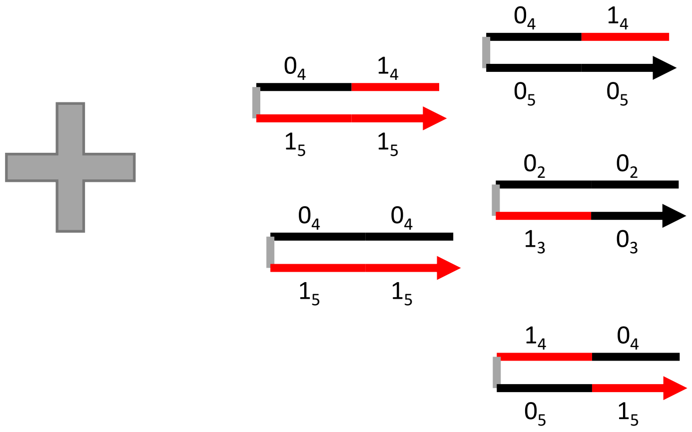

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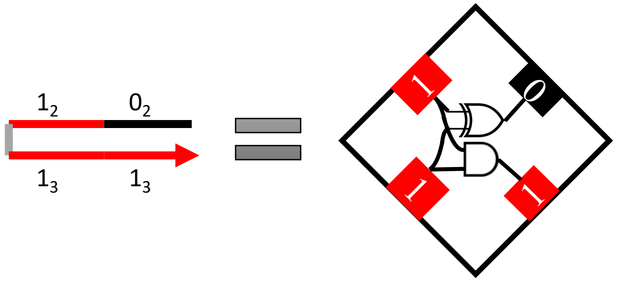
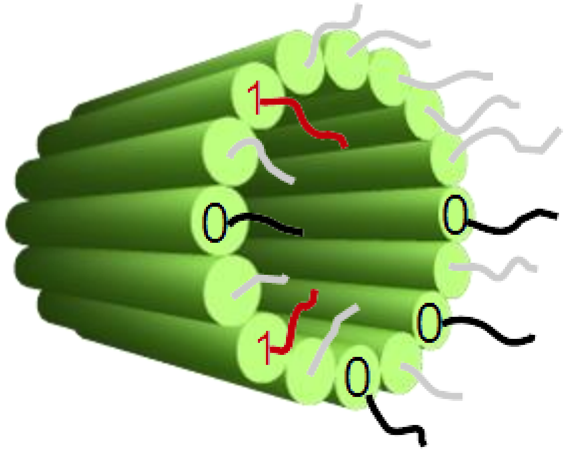
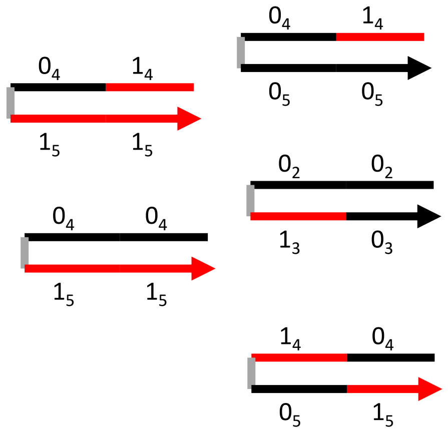


DNA origami seed

single-stranded "input-adapter" extensions encoding 6 input bits

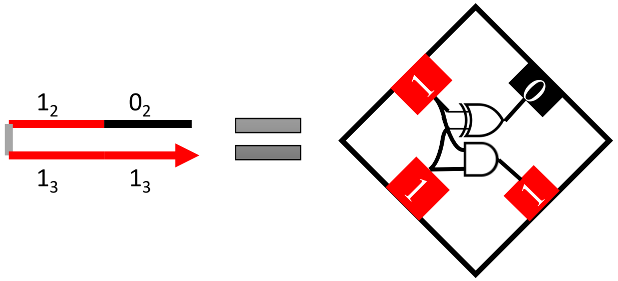


single-stranded tiles implementing circuit gates



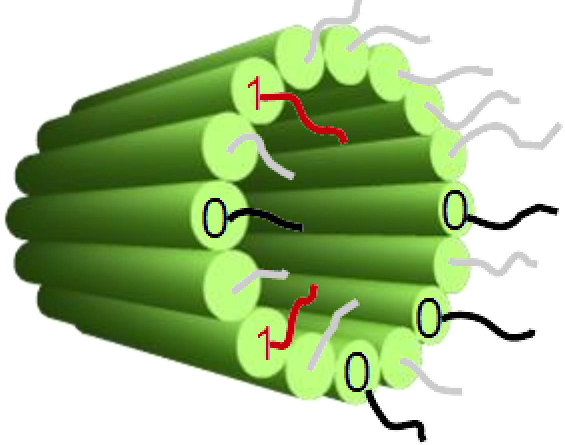
need barrier to nucleation (tile growth without seed);
[tile]=100 nM;
temperature=50.9° C

Seeded growth



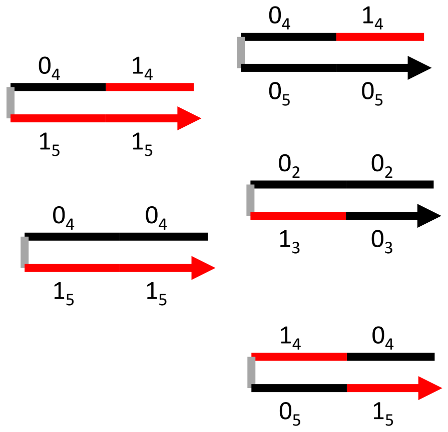
DNA origami seed

single-stranded “input-adapter” extensions encoding 6 input bits



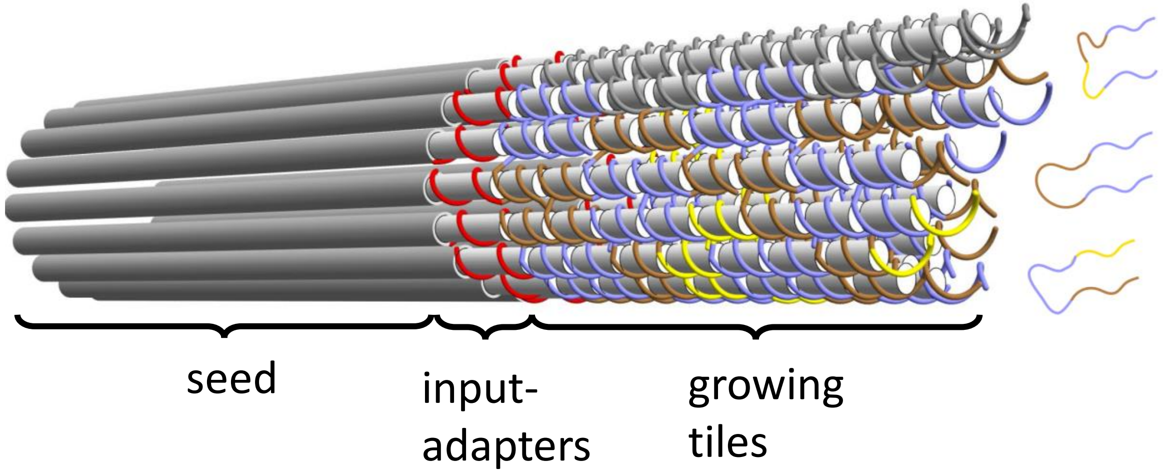
+

single-stranded tiles implementing circuit gates

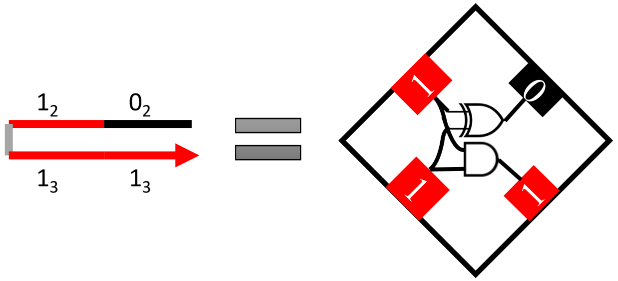


need barrier to <u>nucleation</u> (tile growth without seed);
[tile]=100 nM;
temperature=50.9° C

hold 8-48 hours

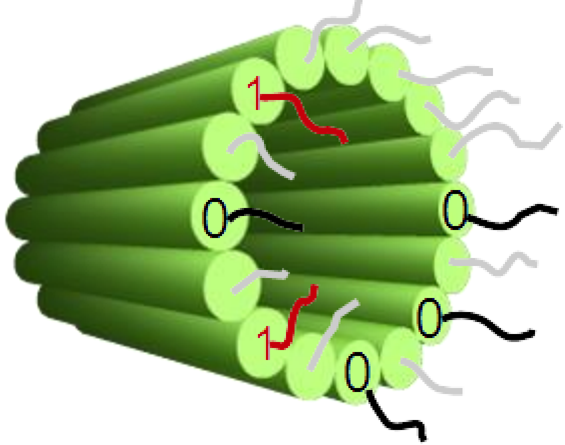


Seeded growth

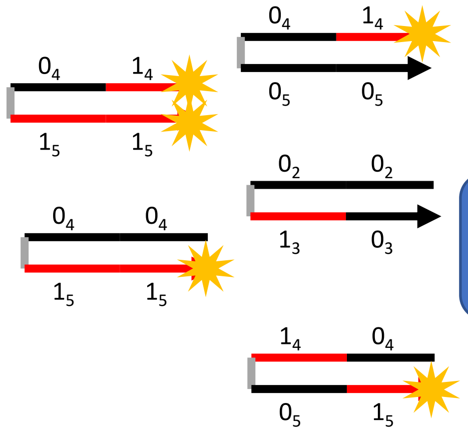


DNA origami seed

single-stranded “input-adapter” extensions encoding 6 input bits



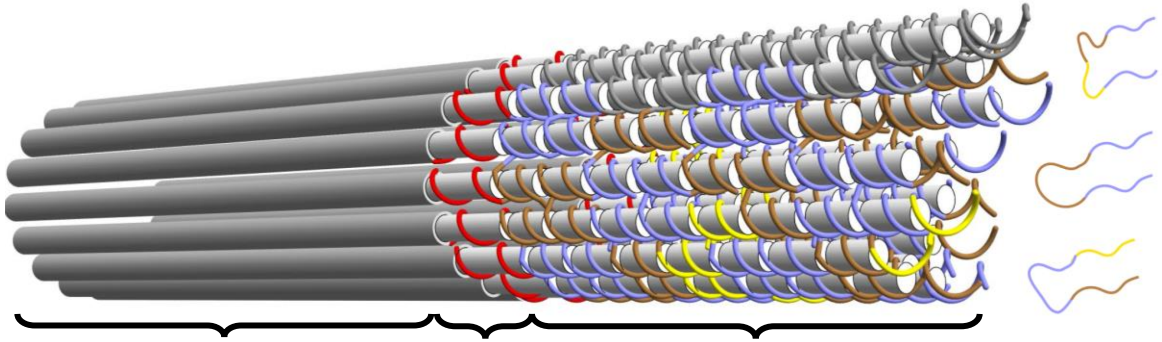
single-stranded tiles implementing circuit gates



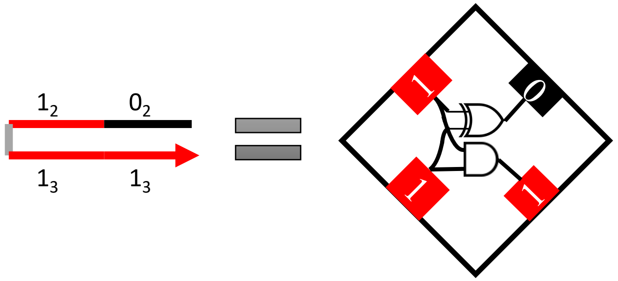
biotins where output = 1

need barrier to <u>nucleation</u> (tile growth without seed); [tile]=100 nM; temperature=50.9° C

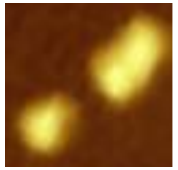
hold 8-48 hours



Seeded growth



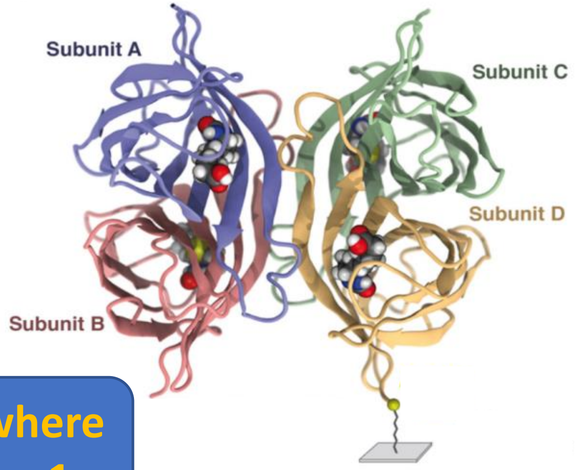
can later add streptavidin (5 nm wide protein) to bind biotins and visualize where the 1's are

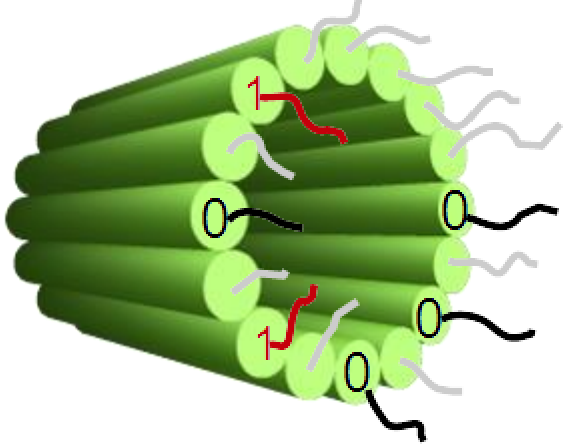


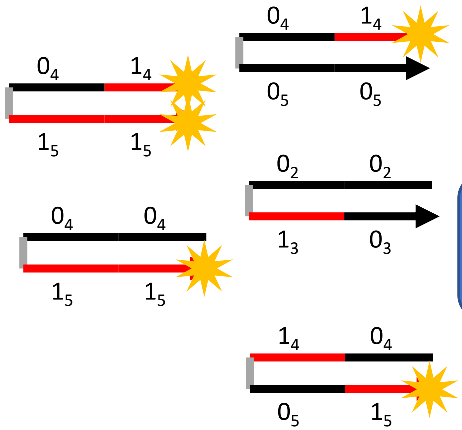
DNA origami seed

single-stranded "input-adapter" extensions encoding 6 input bits

single-stranded tiles implementing circuit gates



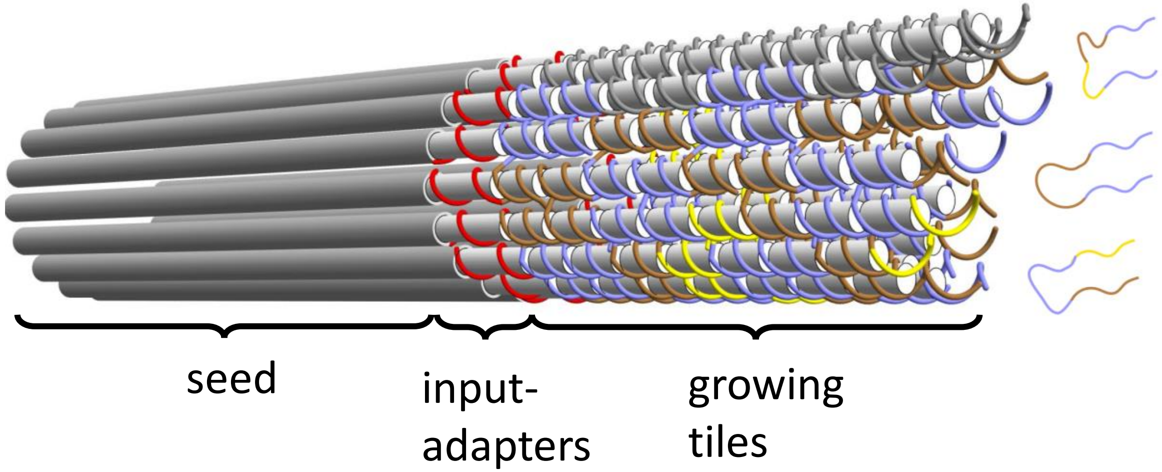




biotins where output = 1

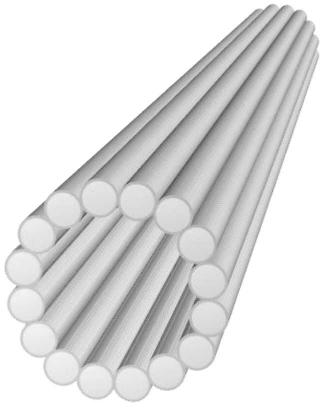
need barrier to <u>nucleation</u> (tile growth without seed); [tile]=100 nM; temperature=50.9° C

hold 8-48 hours

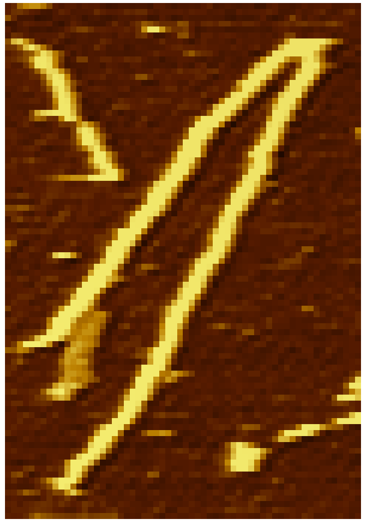


Tubes to ribbons

tube



AFM
image

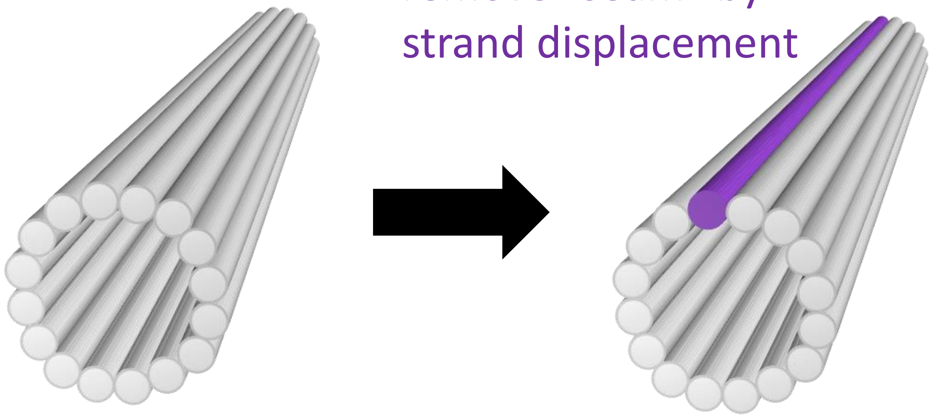


500 nm

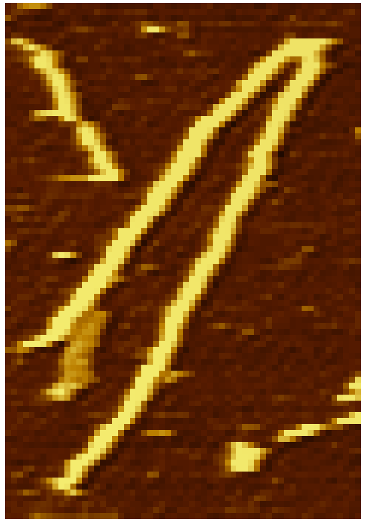
Tubes to ribbons

tube

remove “seam” by
strand displacement

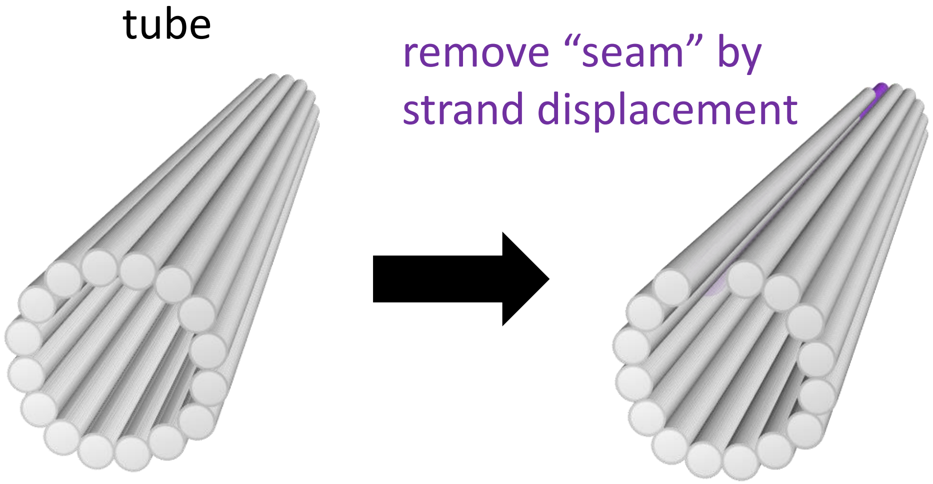


AFM
image

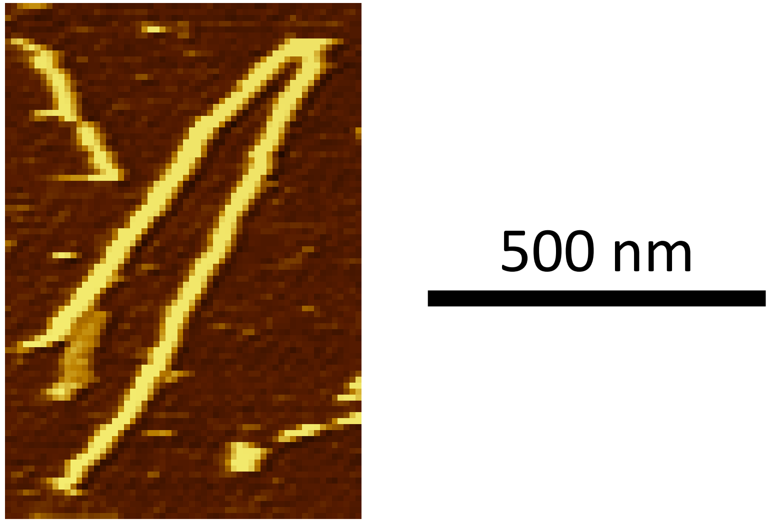


500 nm

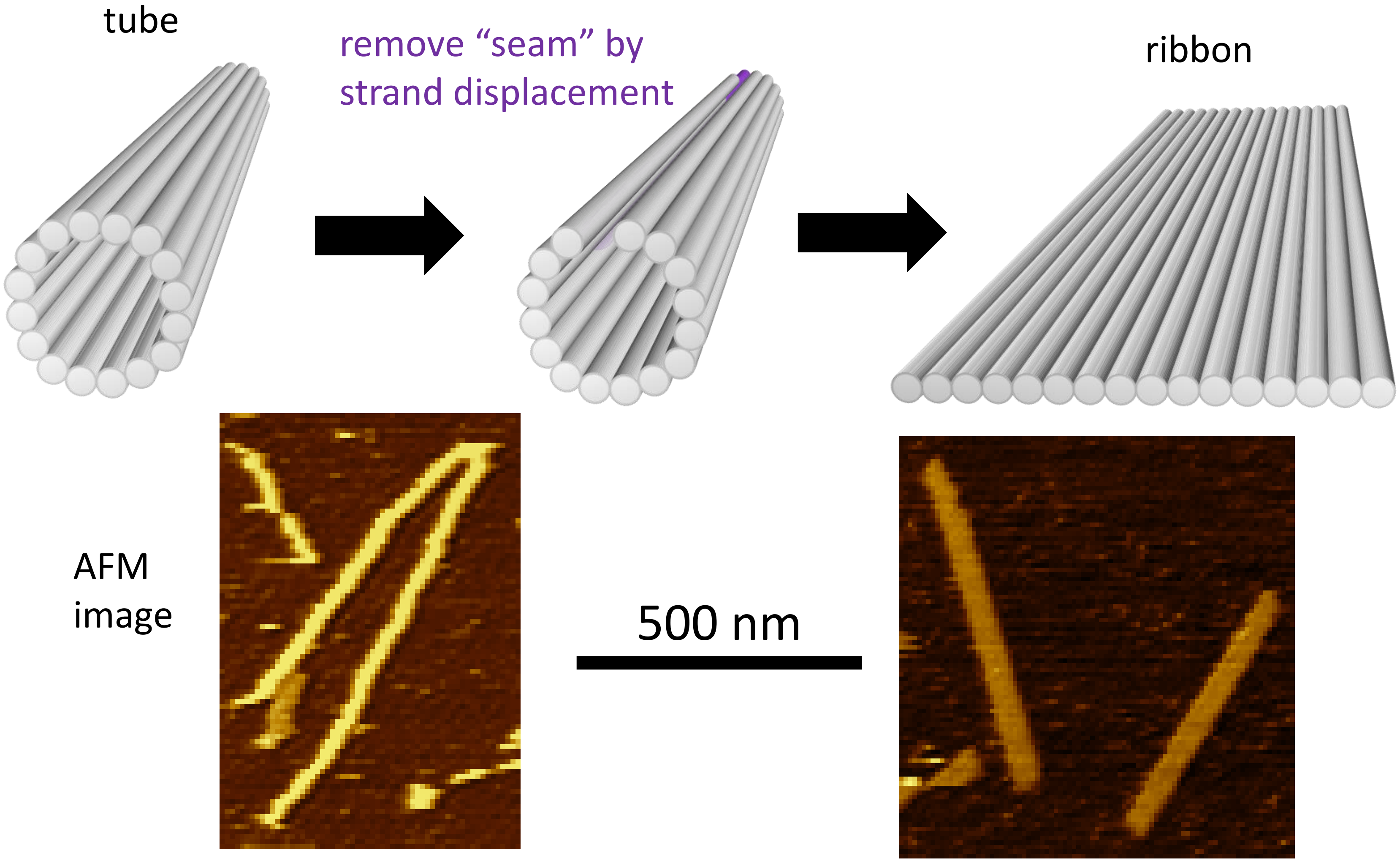
Tubes to ribbons



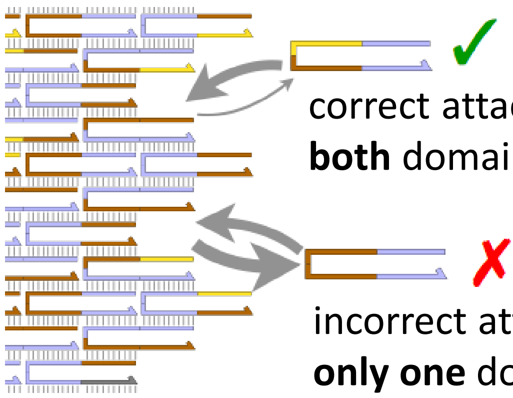
AFM
image



Tubes to ribbons



DNA sequence design

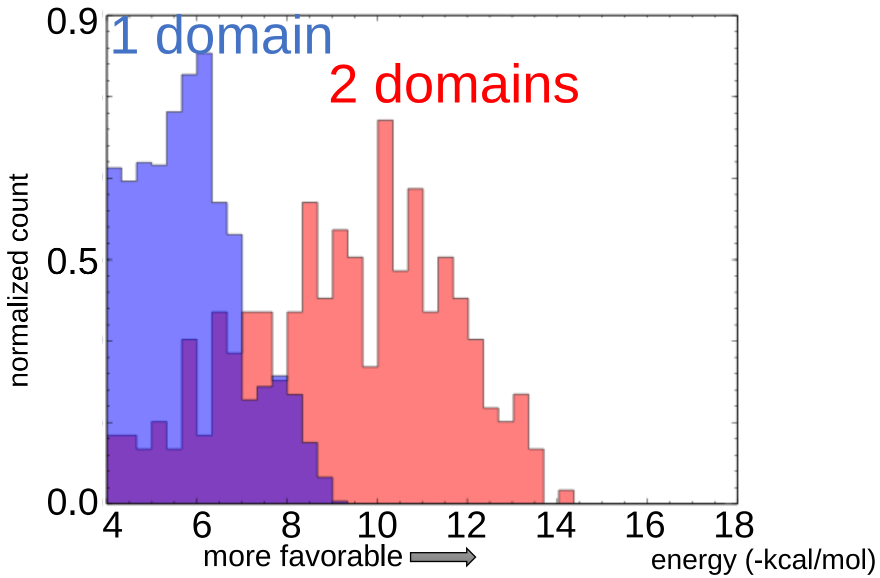


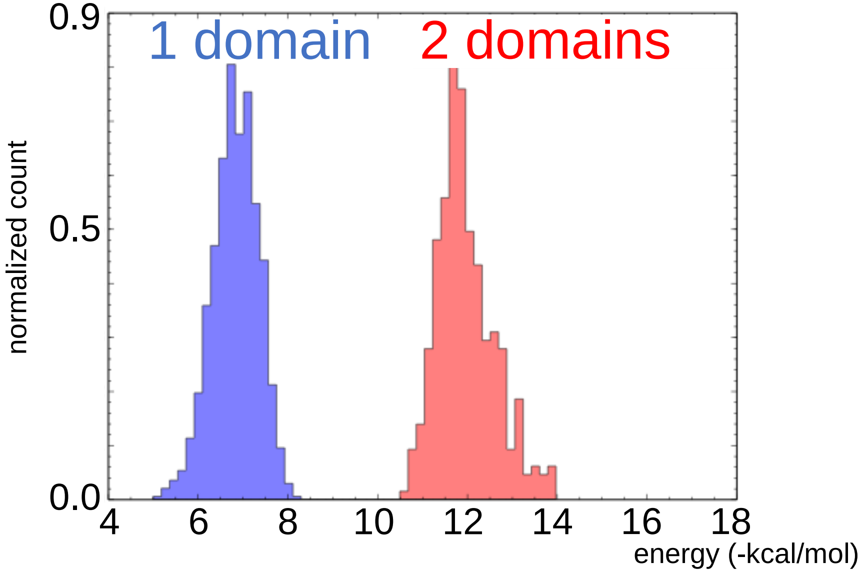
correct attachment:
both domains match

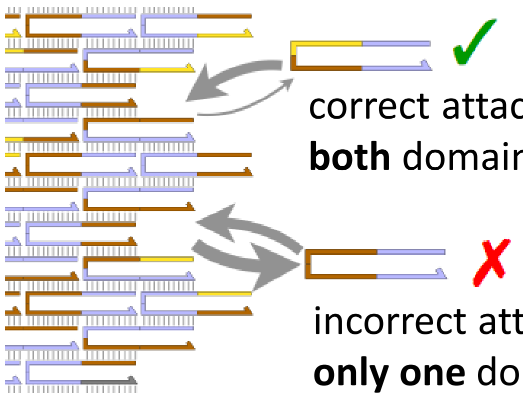
incorrect attachment:
only one domain matches

DNA sequence design

Random sequences vs designed sequences





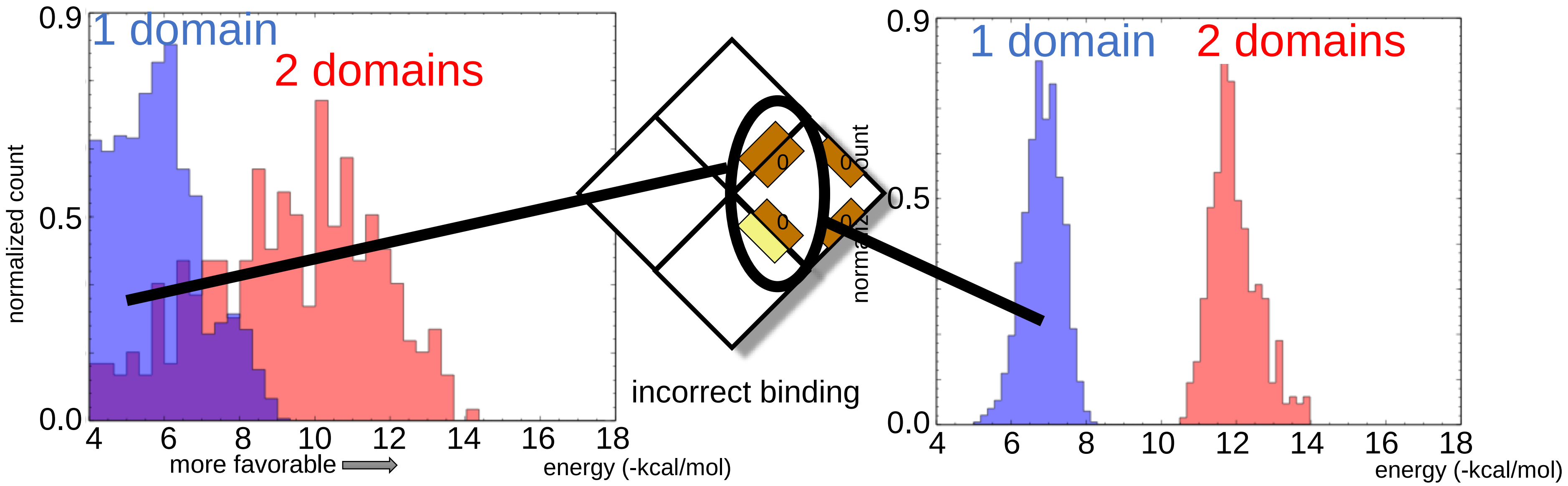


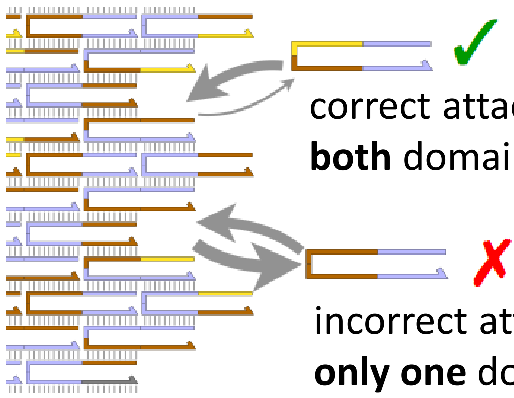
correct attachment:
both domains match

incorrect attachment:
only one domain matches

DNA sequence design

Random sequences vs designed sequences





correct attachment:
both domains match

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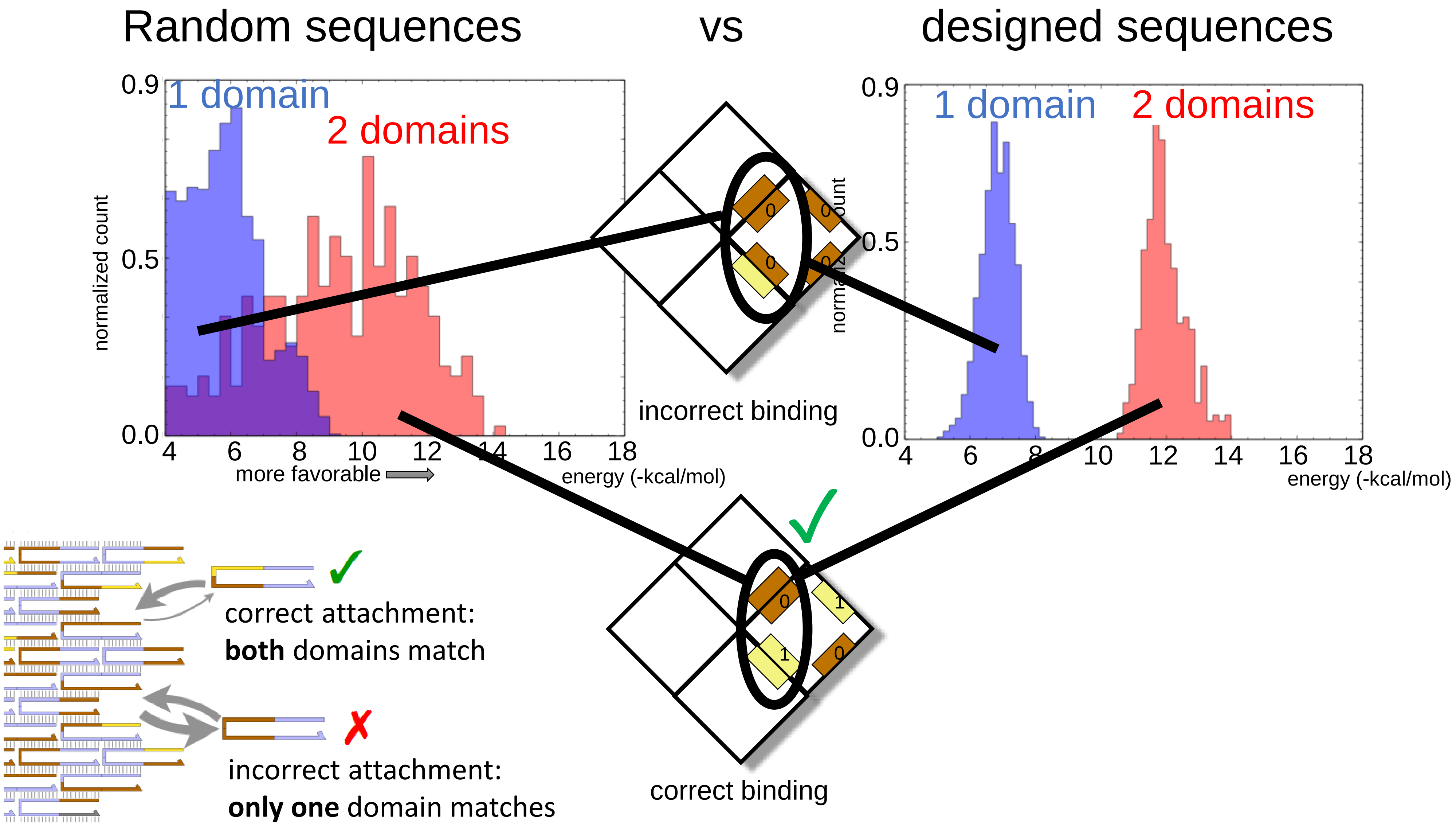
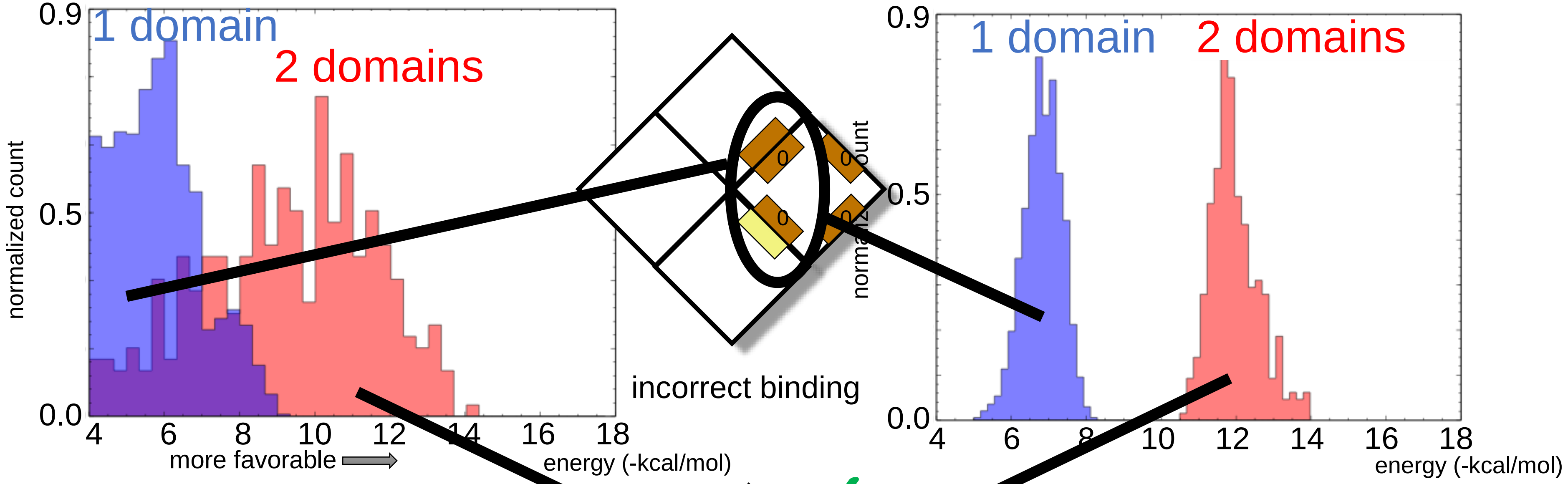
only one domain matches

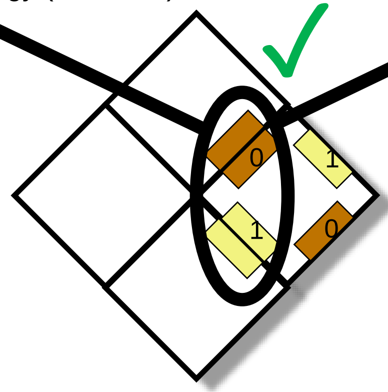
DNA sequence design

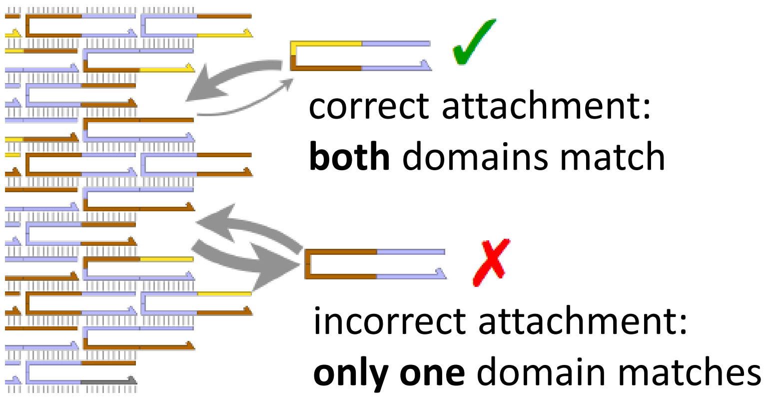


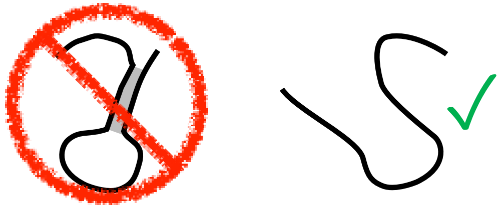
DNA sequence design

Random sequences vs designed sequences





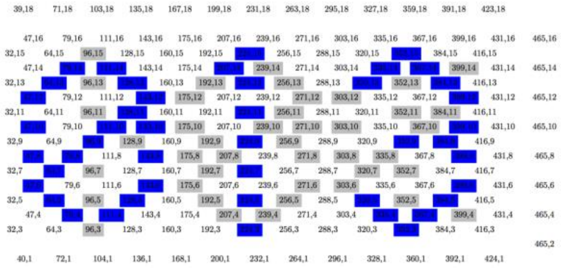




Other goals:

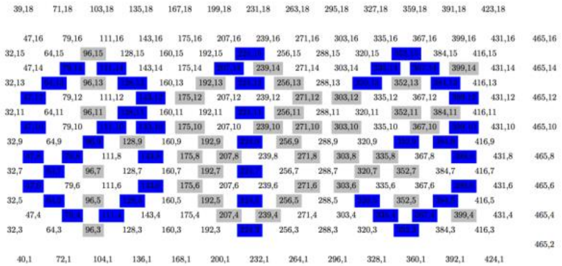
- low strand secondary structure
- low interaction between strands

Bar-coding origami seed for imaging multiple samples at once



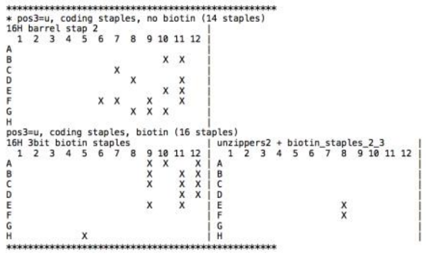
some staples of origami seed have version with a biotin

Bar-coding origami seed for imaging multiple samples at once

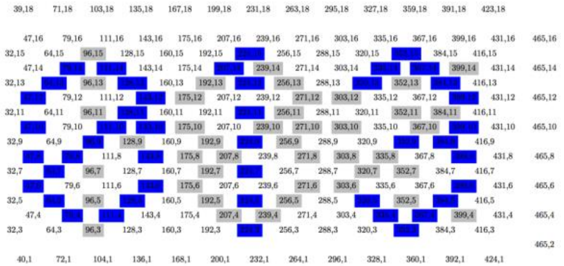


some staples of origami seed have version with a biotin

Generate plate map



Bar-coding origami seed for imaging multiple samples at once



some staples of origami seed have version with a biotin

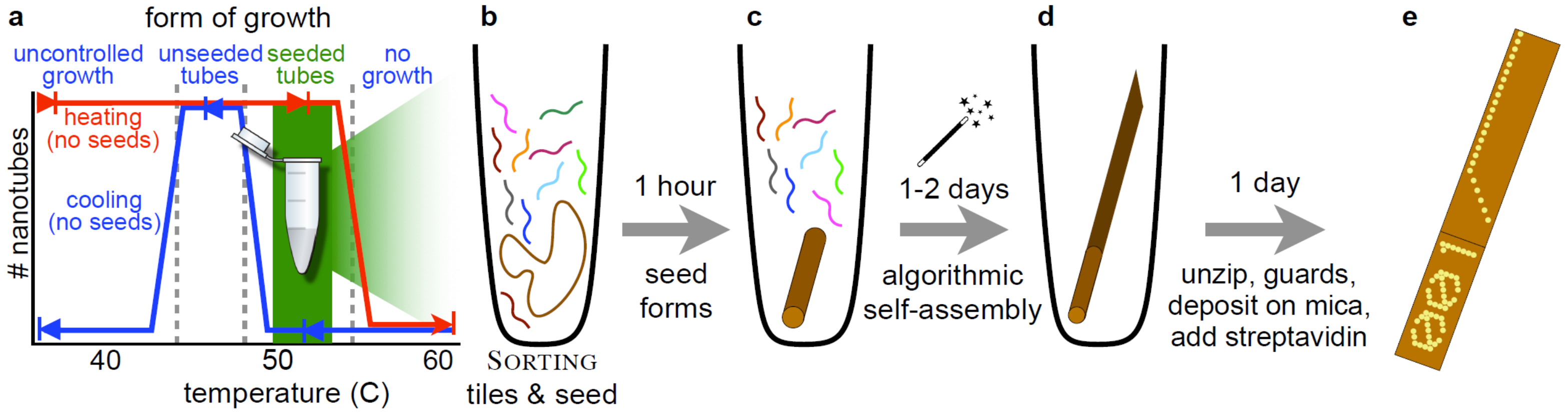
Generate plate map

```
**************************************************
* pos3=u, coding staples, no biotin (14 staples)
16H barrel stap 2                        |
  1  2  3  4  5  6  7  8  9 10 11 12     |
A                                        |
B                          X  X          |
C                   X                    |
D                      X        X        |
E                            X  X        |
F                X  X     X     X        |
G                      X  X  X           |
H                                        |
pos3=u, coding staples, biotin (16 staples)
16H 3bit biotin staples                  | unzippers2 + biotin_staples_2_3 |
  1  2  3  4  5  6  7  8  9 10 11 12     |   1  2  3  4  5  6  7  8  9 10 11 12 |
A                         X  X     X     | A                                    |
B                         X     X  X     | B                                    |
C                         X     X  X     | C                                    |
D                               X  X     | D                                    |
E                         X     X        | E                      X             |
F                                        | F                      X             |
G                                        | G                                    |
H             X                          | H                                    |
**************************************************
```

represents some combination of circuit and input, e.g.,
013 = *"parity circuit, input=011010"*

label with streptavidin

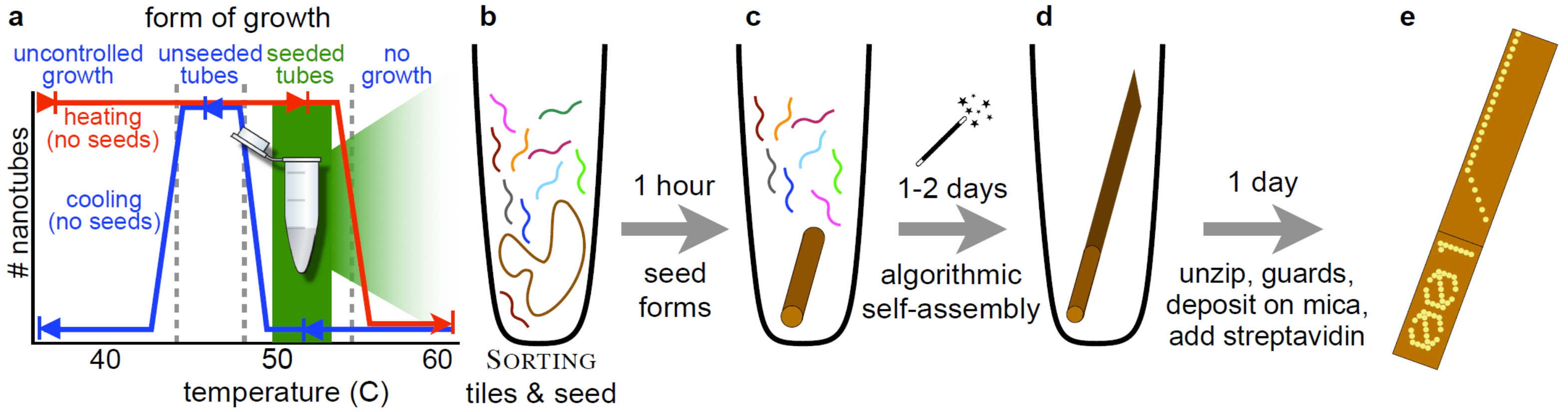
Experimental protocol



To execute circuit γ on input $x \in \{0,1\}^*$:

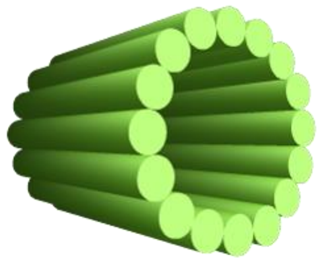
- Mix

Experimental protocol

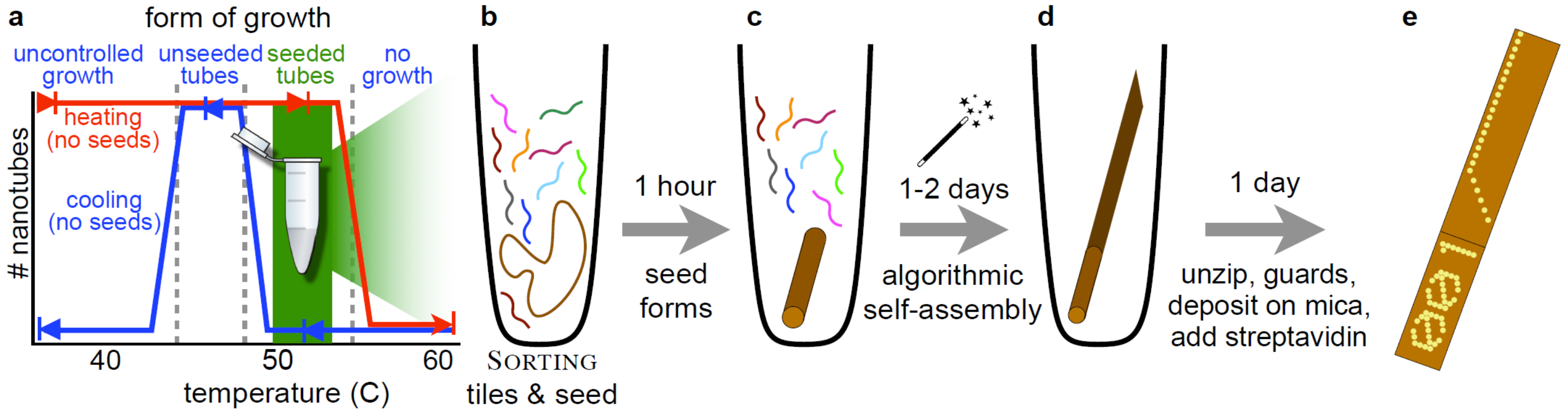


To execute circuit γ on input $x \in \{0,1\}^*$:

- Mix
  - origami seed (bar-coded to identify γ and x)

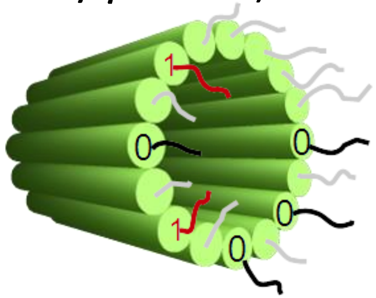


Experimental protocol

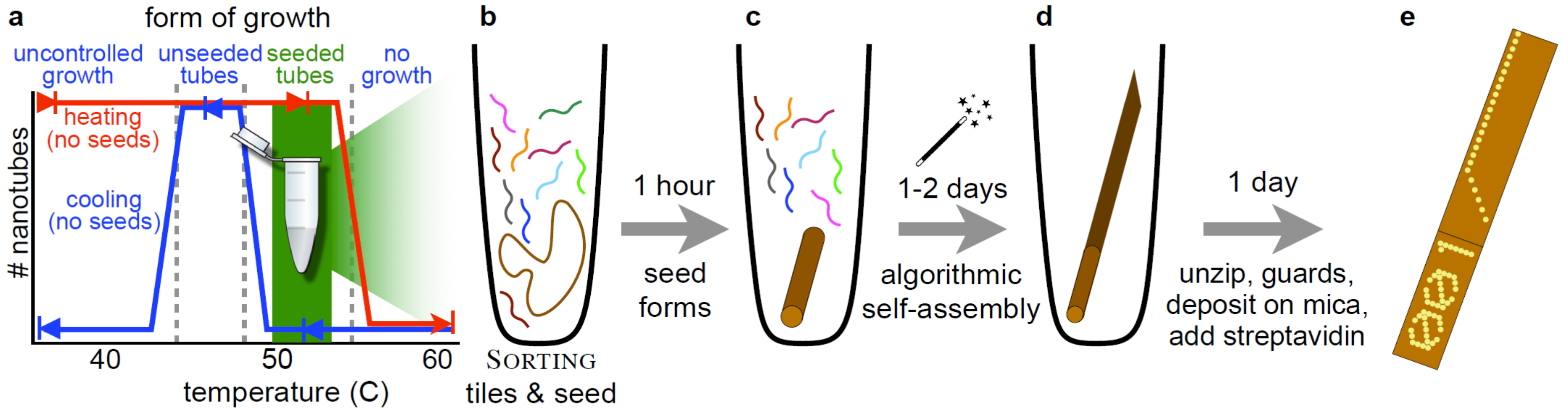


To execute circuit γ on input $x \in \{0,1\}^*$:

- Mix
  - origami seed (bar-coded to identify γ and x)
  - "adapter" strands encoding x

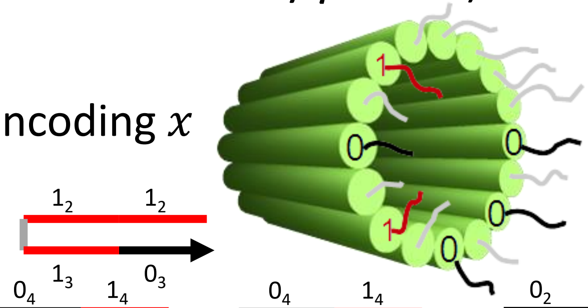


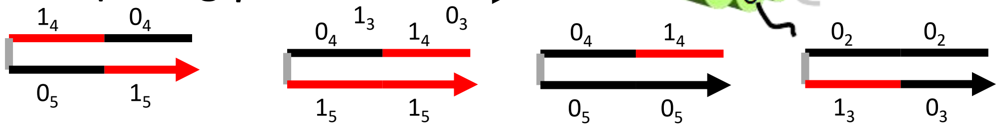
Experimental protocol



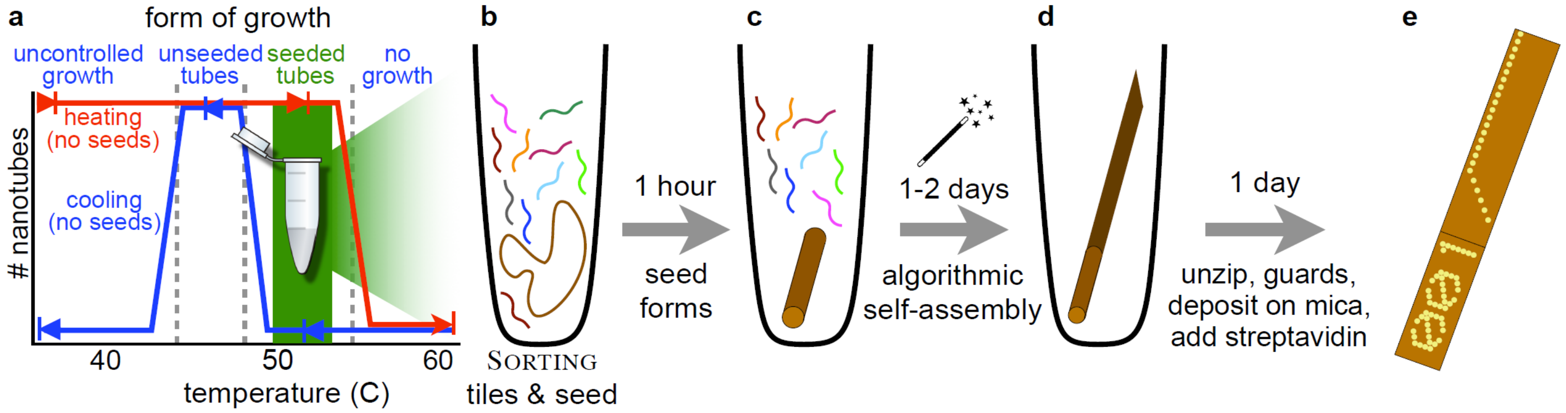
To execute circuit γ on input $x \in \{0,1\}^*$:

- Mix
  - origami seed (bar-coded to identify γ and x)
  - “adapter” strands encoding x
  - tiles computing γ



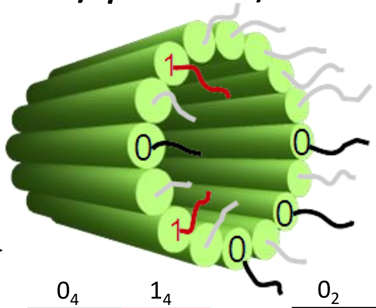


Experimental protocol

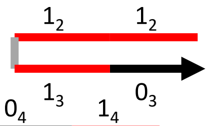


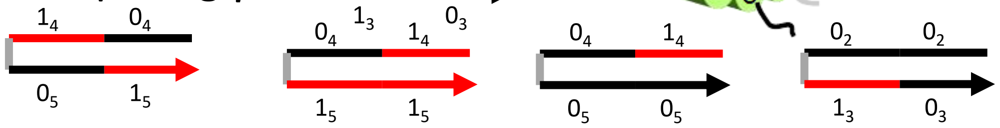
To execute circuit γ on input $x \in \{0,1\}^*$:

- Mix
  - origami seed (bar-coded to identify γ and x)



  - "adapter" strands encoding x
  - tiles computing γ



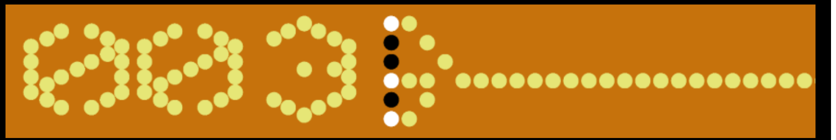


- Anneal 90° C to 50.9° C in 1 hour (*origami seeds form*)
- Hold at 50.9° C for 1-2 days (*tiles grow tubes from seed*)
- Add "unzipper" strands (remove seam to convert tube to ribbon)
- Add "guard" strands (complements of output sticky ends, to deactivate tiles)
- Deposit on mica, buffer wash, add streptavidin, AFM

Results

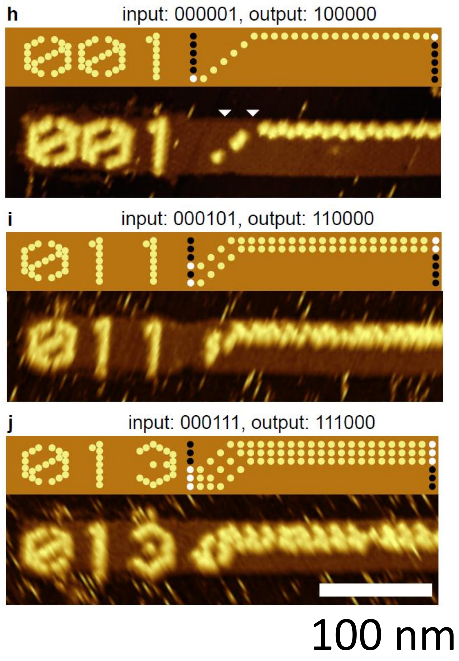
```
def test_parity():
    actual = parity('100101')

    expected =
```

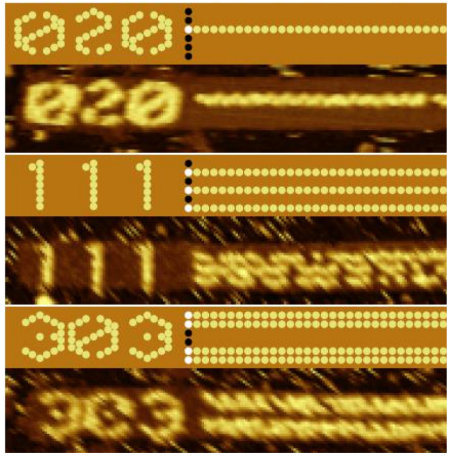


```
    assertEquals(expected, actual)
```

SORTING

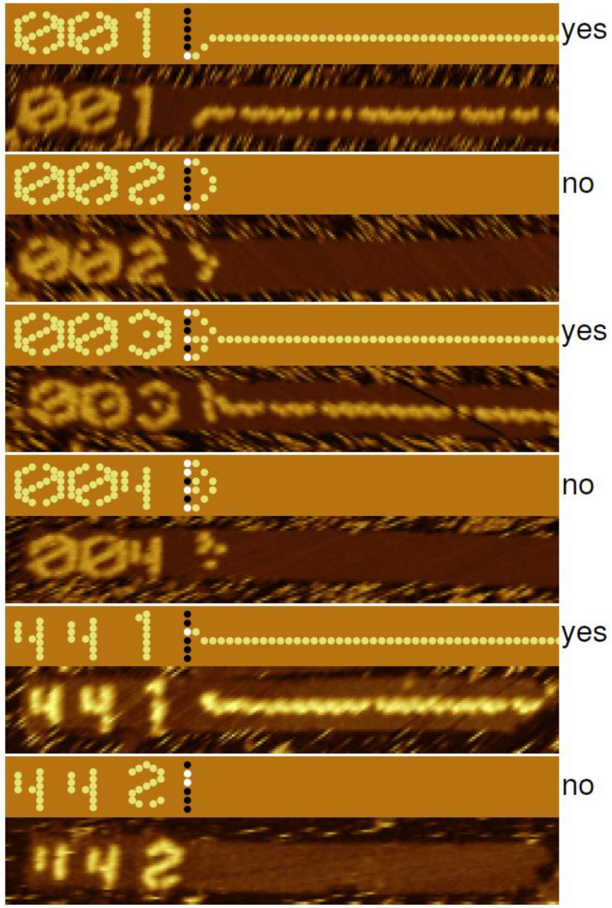


COPY



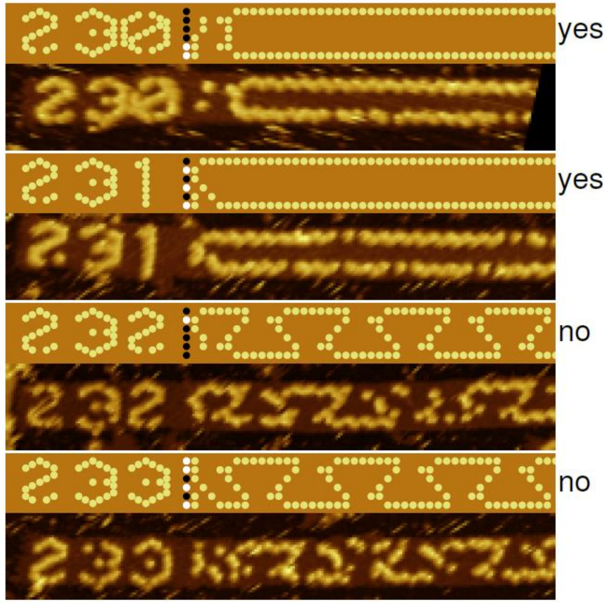
PARITY

Is the number of 1's odd?



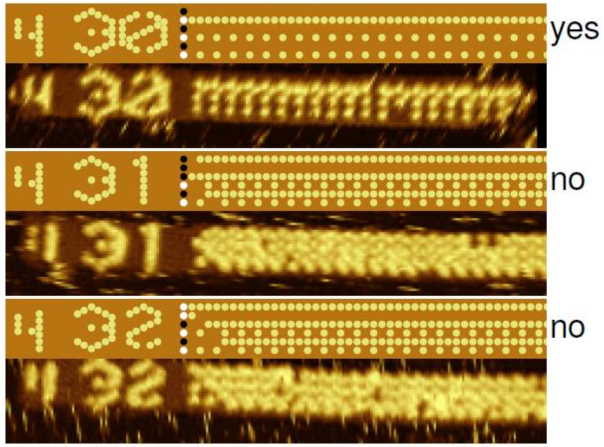
MULTIPLEOF3

Is the input binary number a multiple of 3?



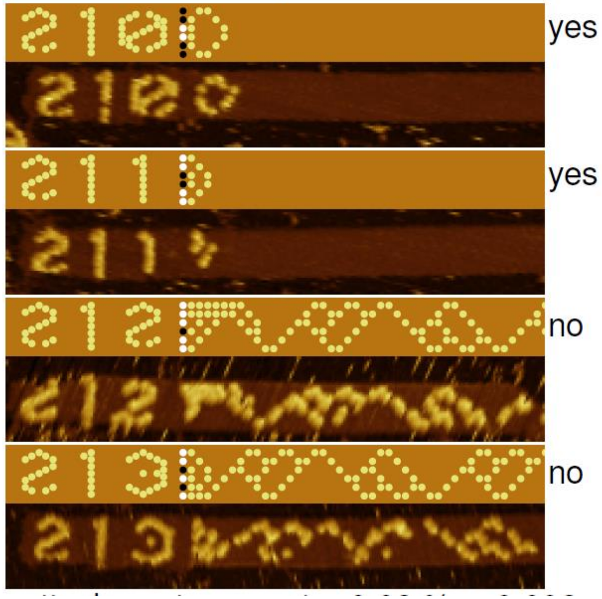
RECOGNISE21

Is the binary input = 21?



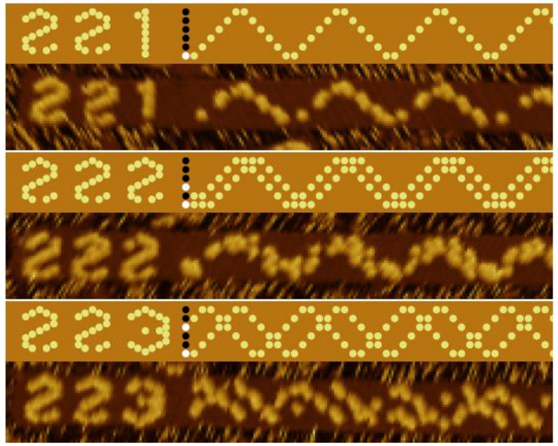
PALINDROME

Is the input a palindrome?

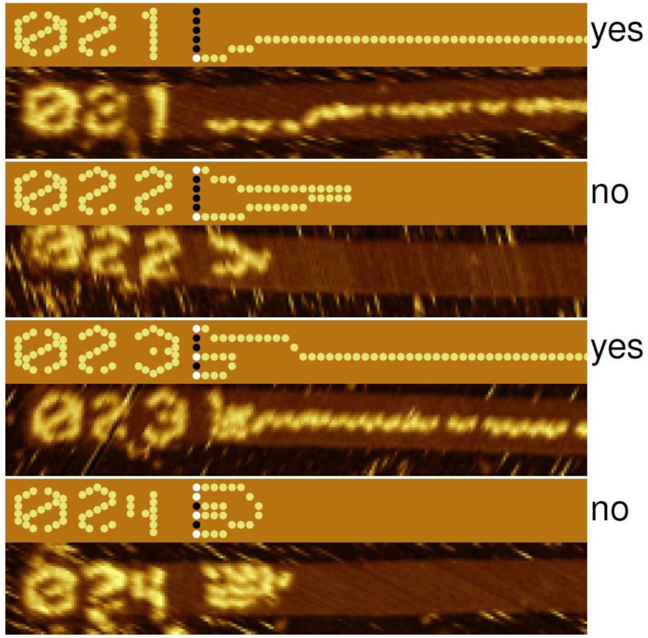


ZIG-ZAG

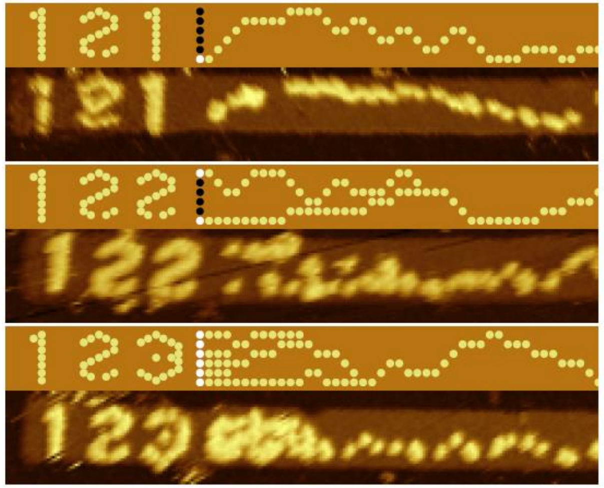
Repeating pattern



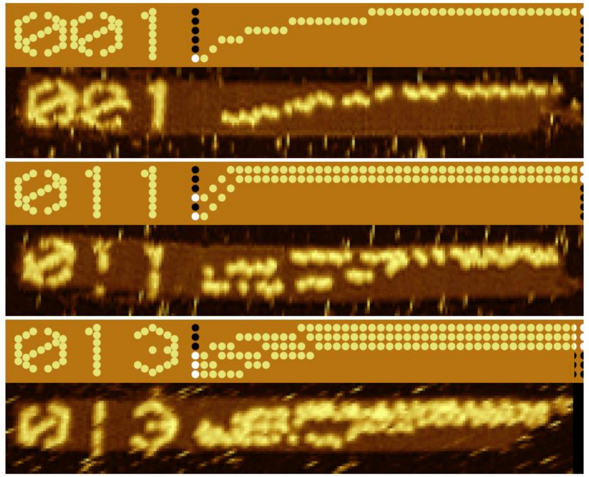
LazyParity



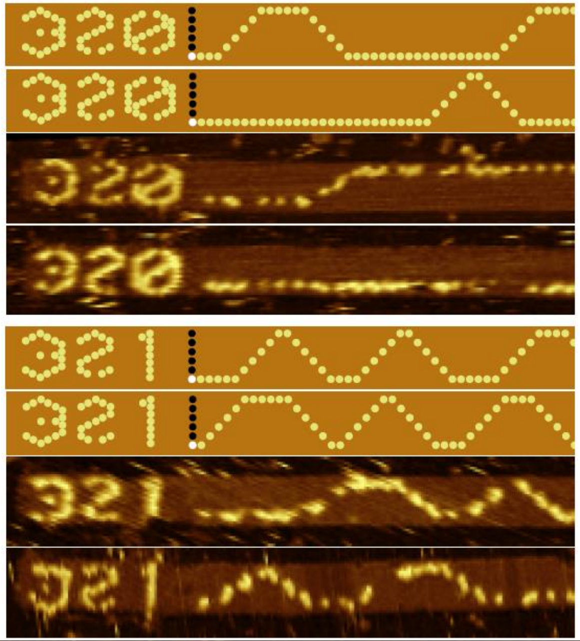
LeaderElection



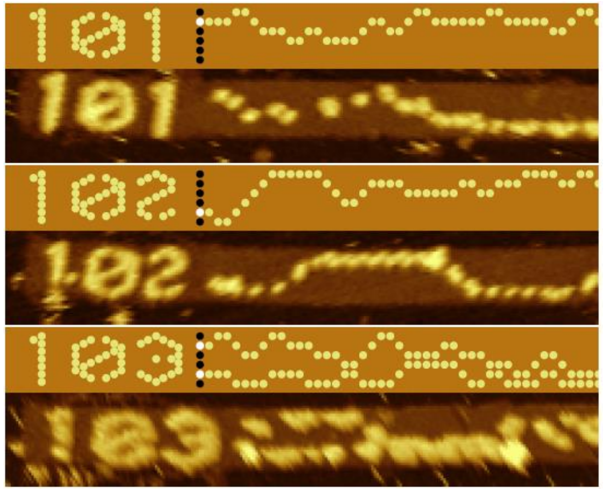
LazySorting



Waves

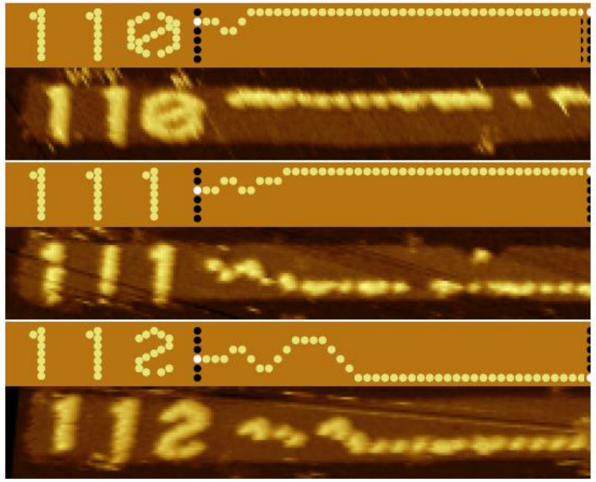


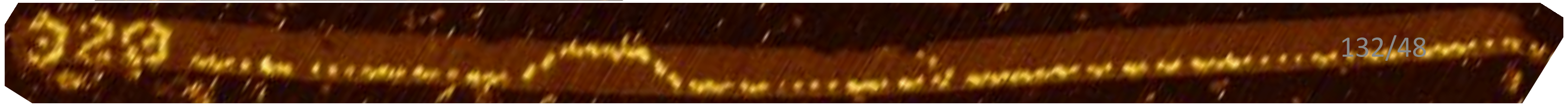
RandomWalkingBit



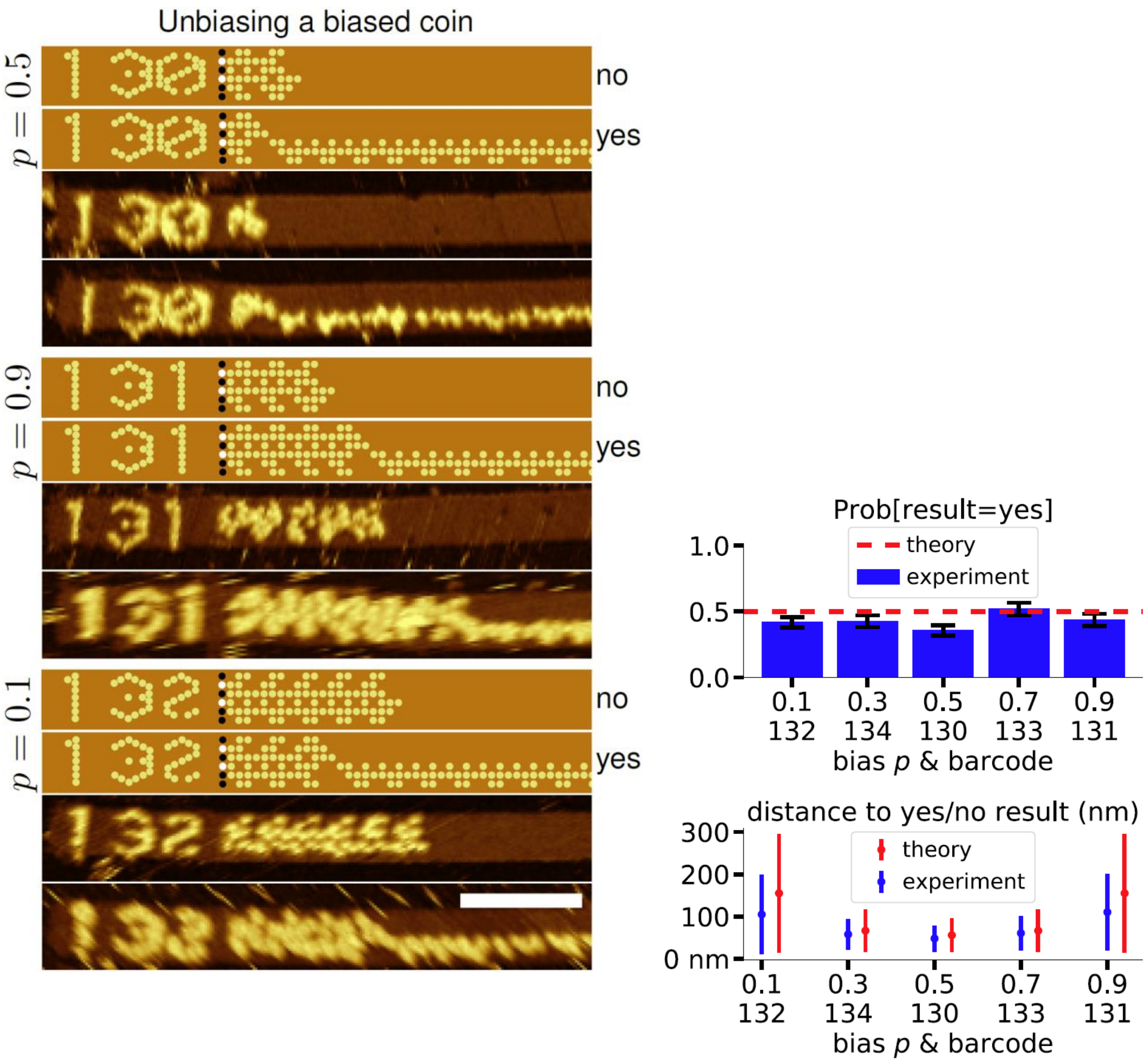
AbsorbingRandomWalkingBit

Random walker absorbs to top/bottom

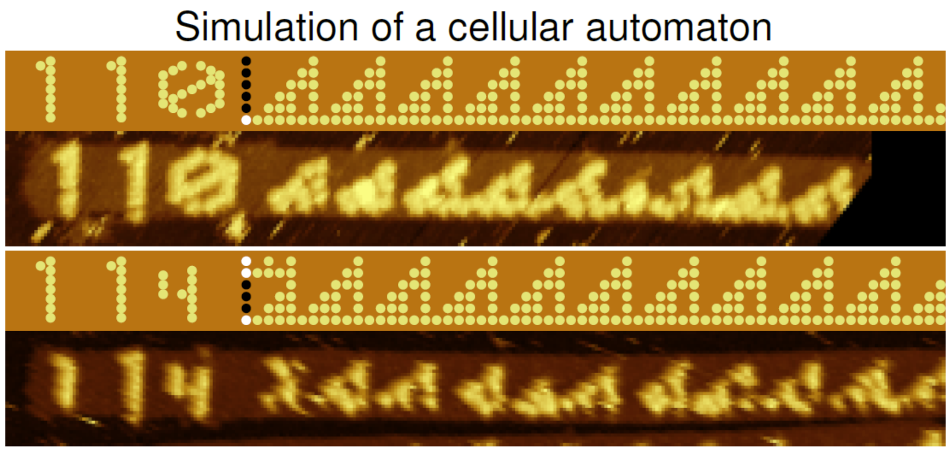




FairCoin



Rule110



Counting to 63

Circuit with 63 distinct strings

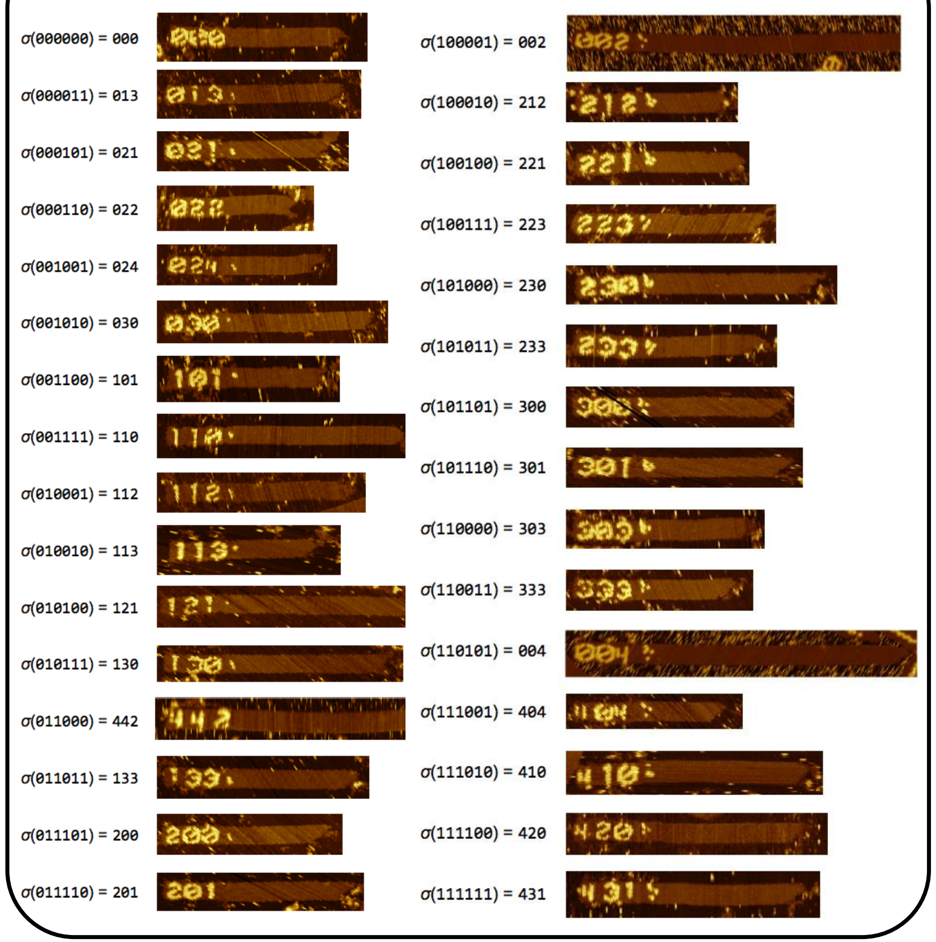
Is there a 64-counter?

No!
Proof by Tristan Stérin, Maynooth University
Consequence of following theorem:
No Boolean function computes an odd permutation if some output bit does not depend on all input bits.

Parity tested on all inputs

2^6 = 64 inputs with 6 bits

32 inputs with even # of 1's



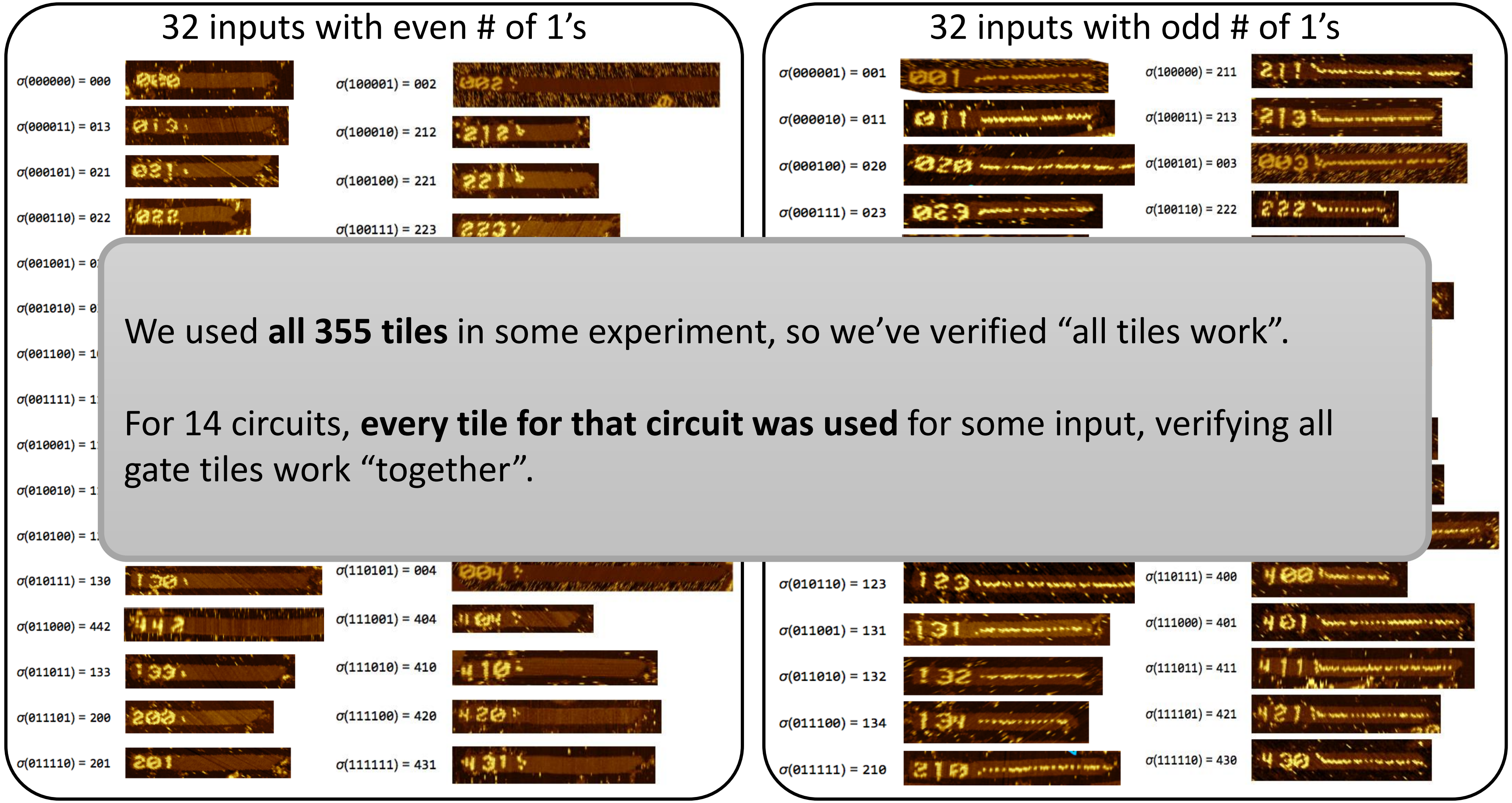
32 inputs with odd # of 1's

σ(6-bit input) = 3-digit barcode representing that input

150 nm

Parity tested on all inputs

$2^6 = 64$ inputs with 6 bits



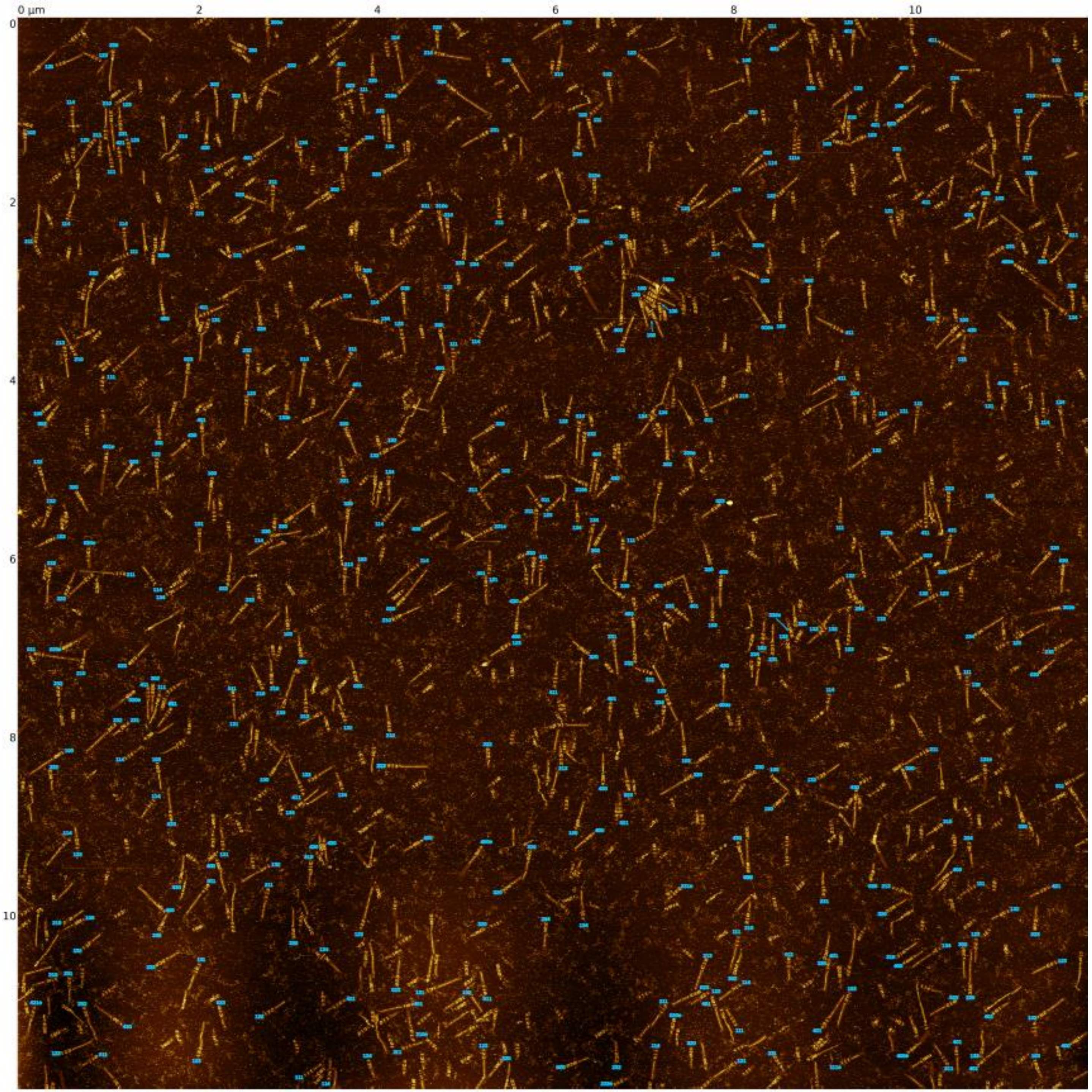
We used **all 355 tiles** in some experiment, so we've verified "all tiles work".

For 14 circuits, **every tile for that circuit was used** for some input, verifying all gate tiles work "together".

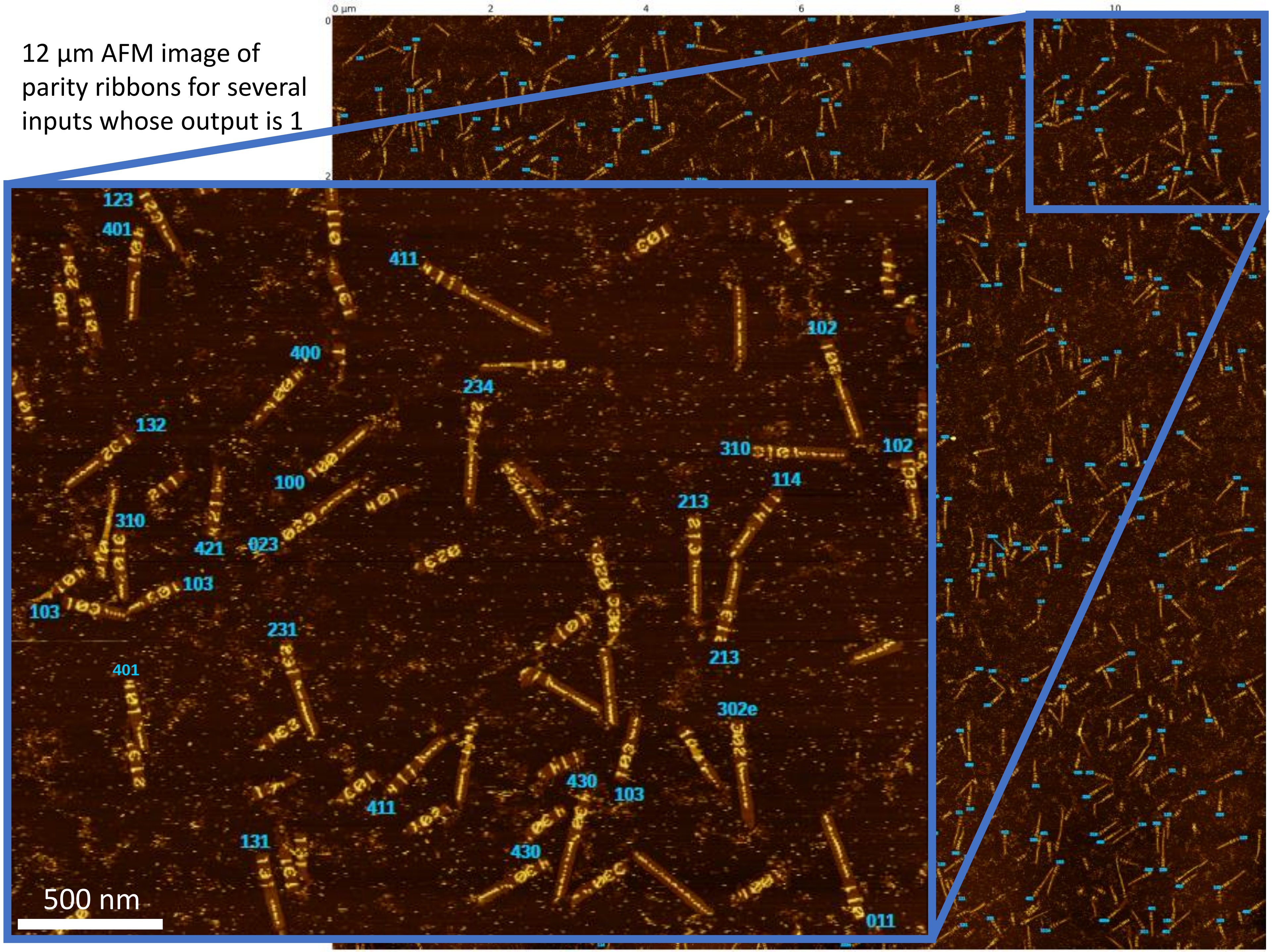
σ(6-bit input) = 3-digit barcode representing that input

150 nm

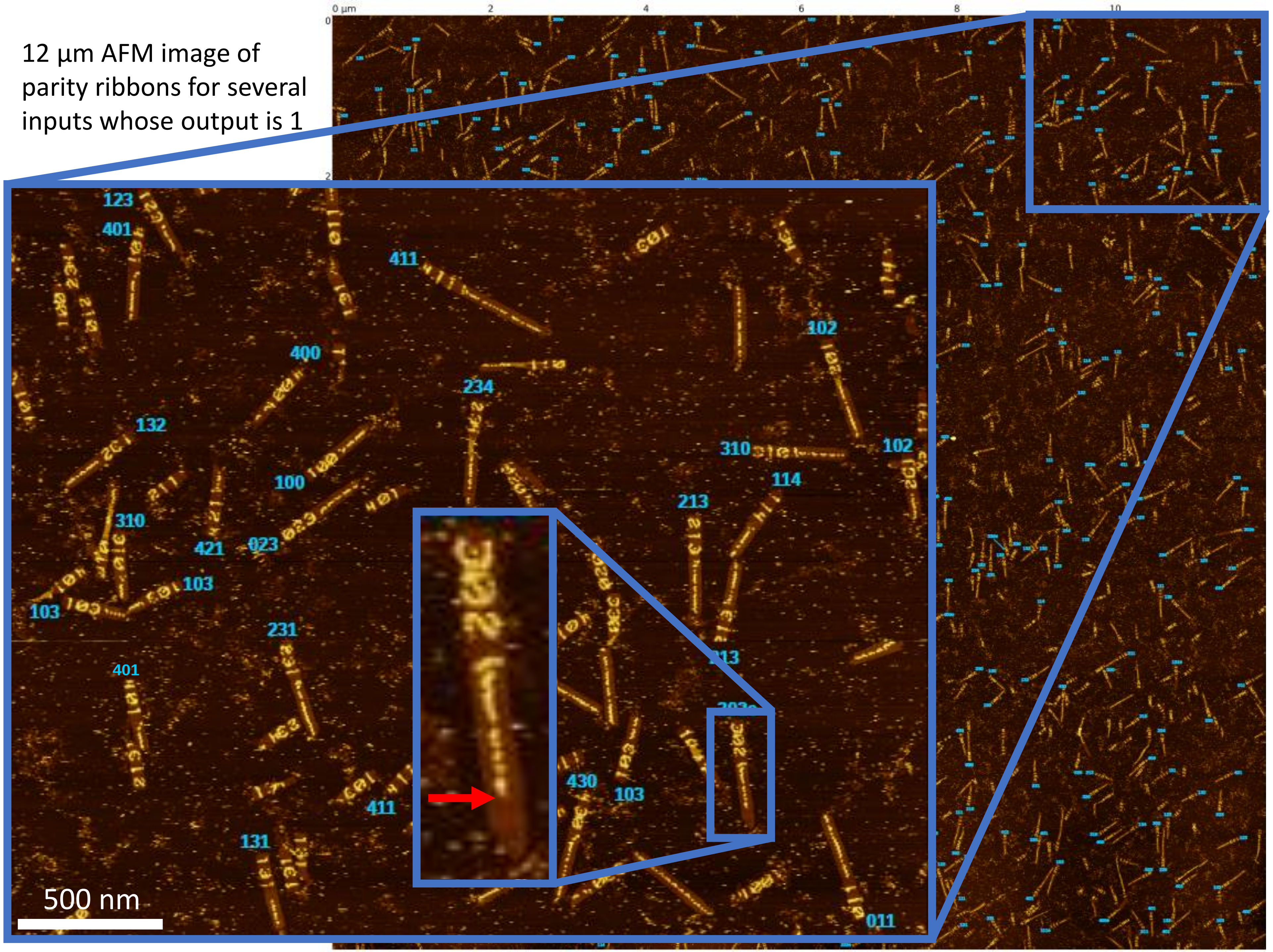
12 µm AFM image of parity ribbons for several inputs whose output is 1



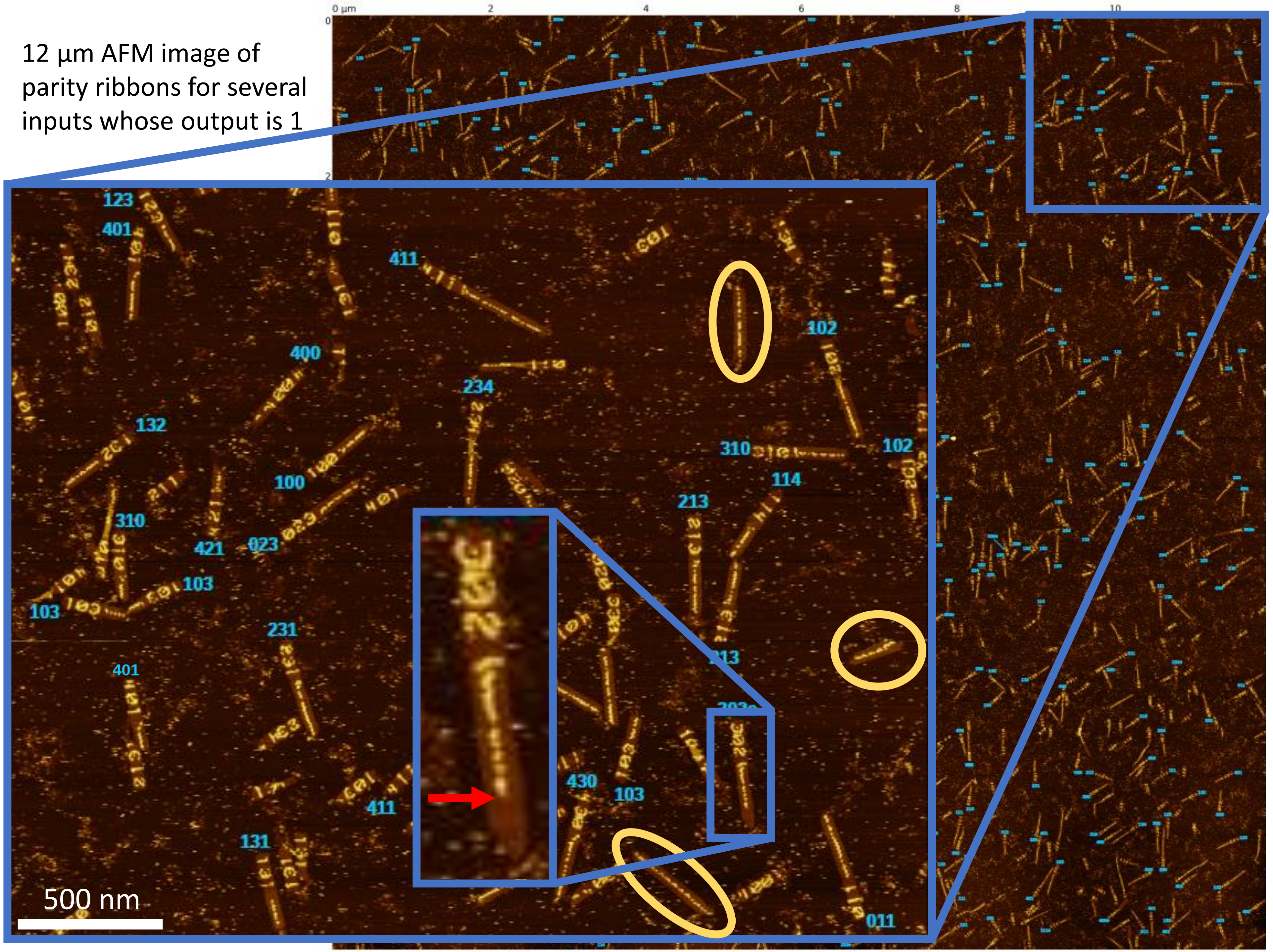
12 µm AFM image of parity ribbons for several inputs whose output is 1



12 µm AFM image of parity ribbons for several inputs whose output is 1



12 μm AFM image of parity ribbons for several inputs whose output is 1



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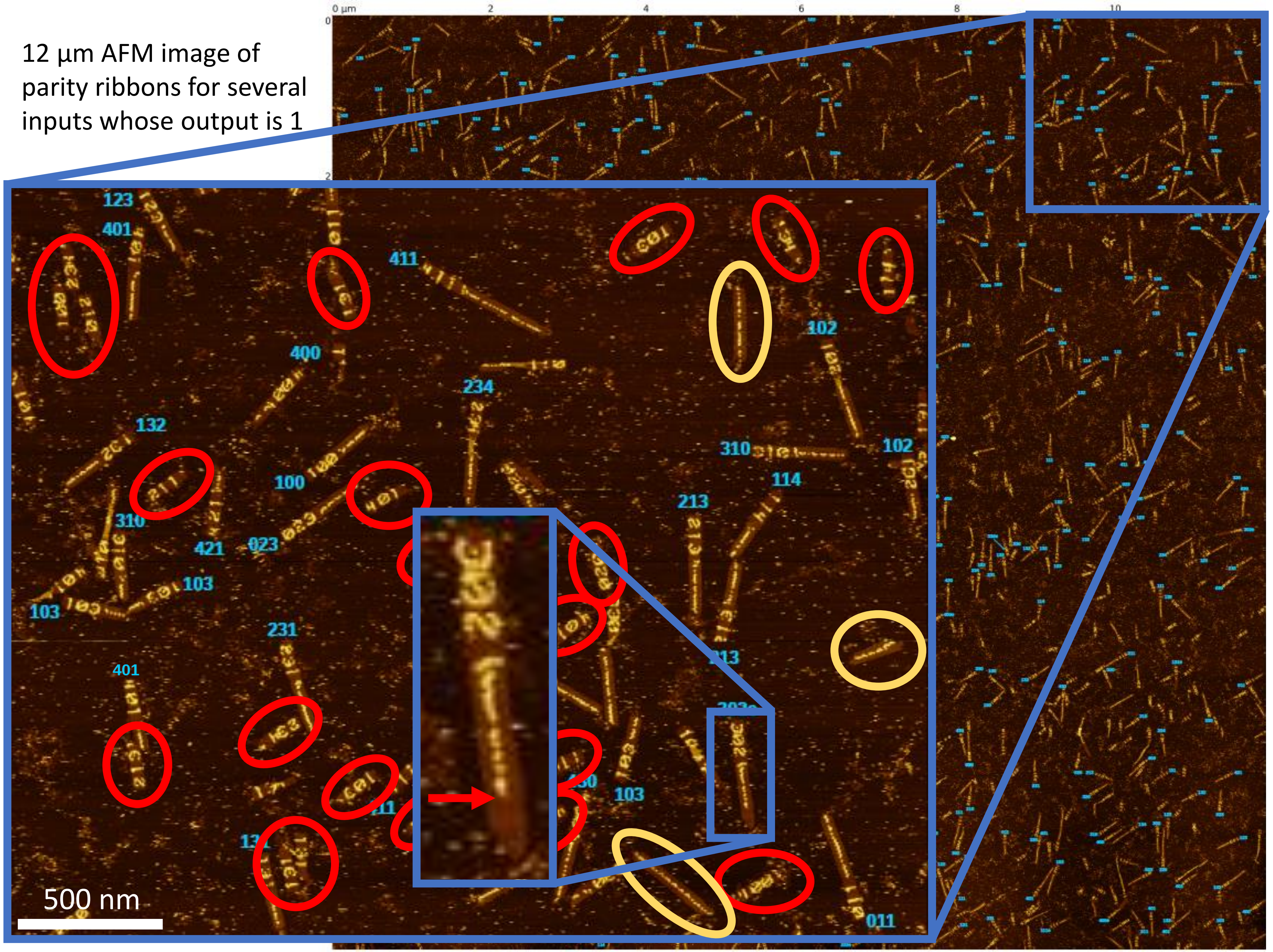

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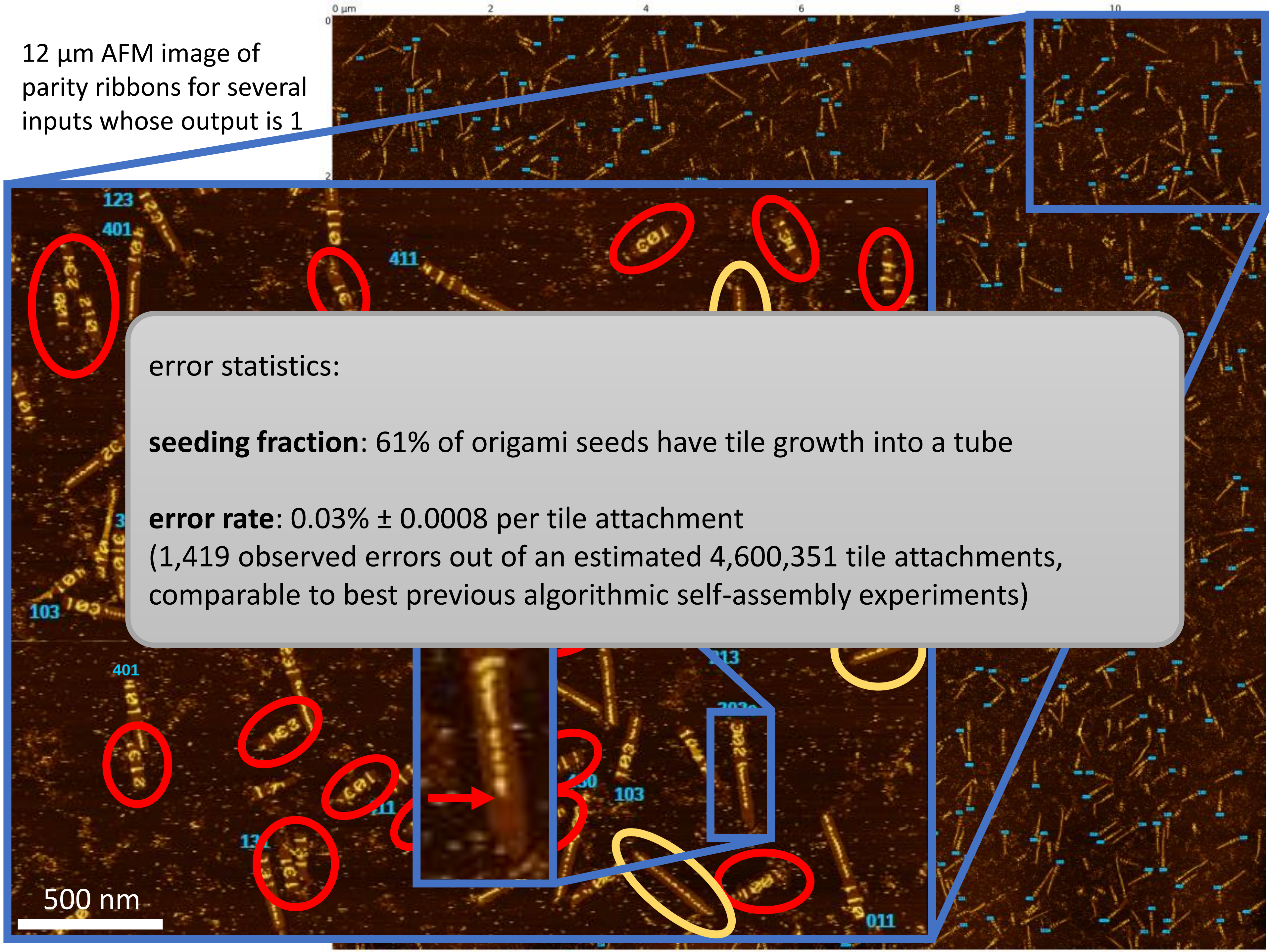

error statistics:

seeding fraction: 61% of origami seeds have tile growth into a tube

error rate: 0.03% ± 0.0008 per tile attachment
(1,419 observed errors out of an estimated 4,600,351 tile attachments, comparable to best previous algorithmic self-assembly experiments)

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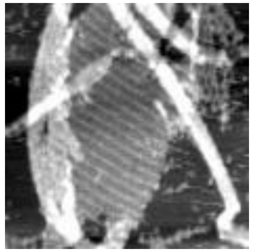

2D tile lattices
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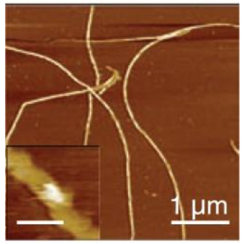

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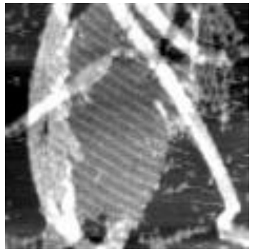

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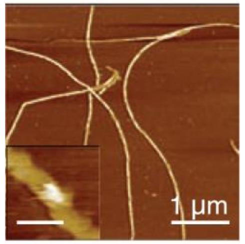

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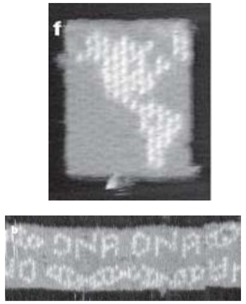

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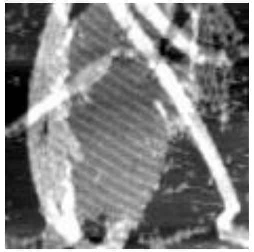

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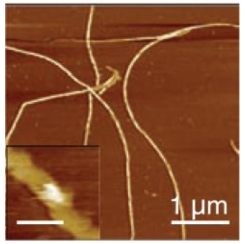

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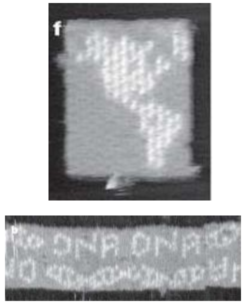

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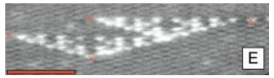
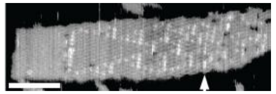
order of magnitude more tile types available than previous **algorithmic** self-assembly

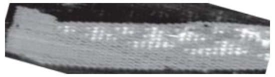
double-crossover tile lattices



(Rothemund et al., *PLoS Bio* 2004)



(Fujibayashi et al., *Nano Letters* 2008)



(Barish et al., *PNAS* 2009)

(Evans, *Ph.D. thesis* 2014)

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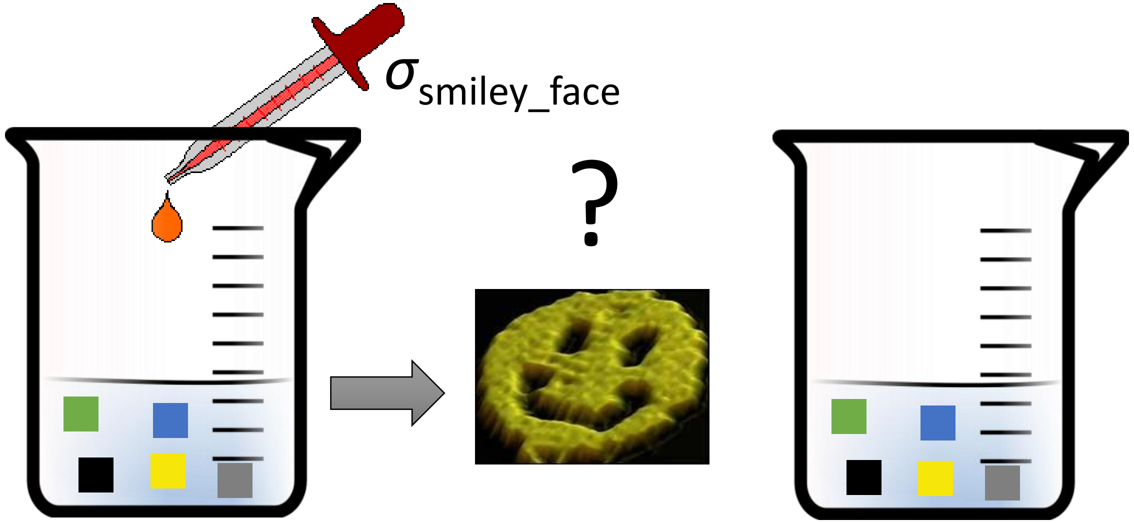

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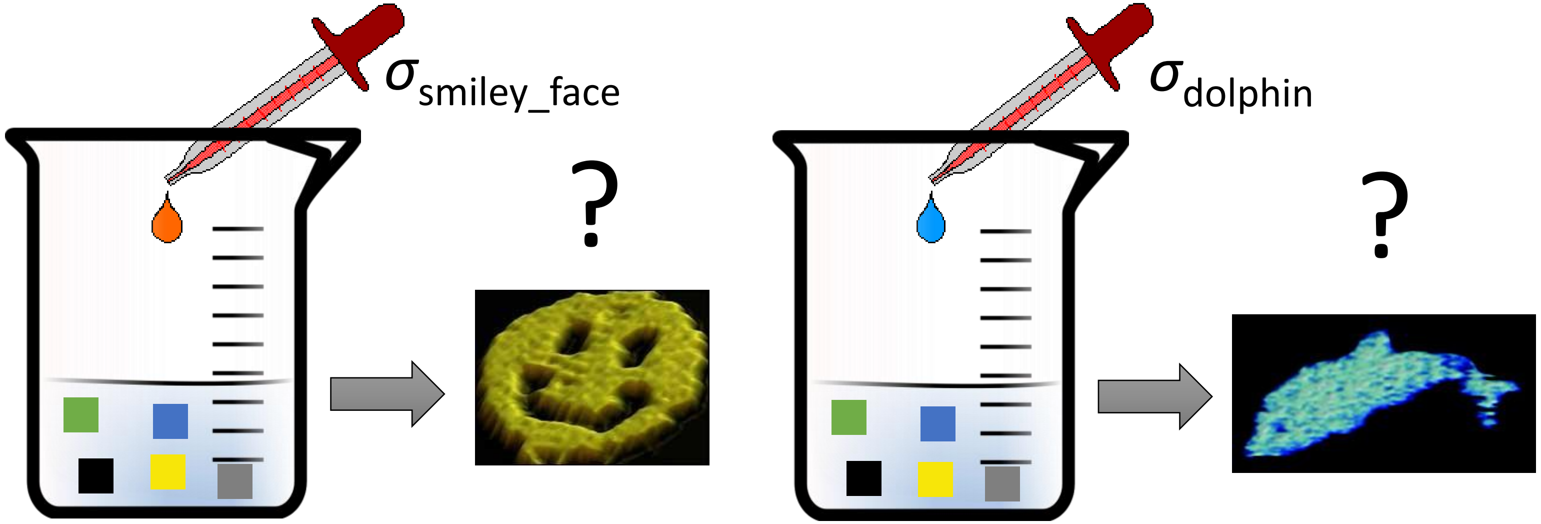

These tiles are universally programmable for building any shape.

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